The American Journal of

CARDIOLOGY

OFFICIAL JOURNAL OF THE American College of Cardiology

Symposium on Catecholamines in Cardiovascular Pathology

W. Raab, M.D.
Guest Editor

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MAY 1960

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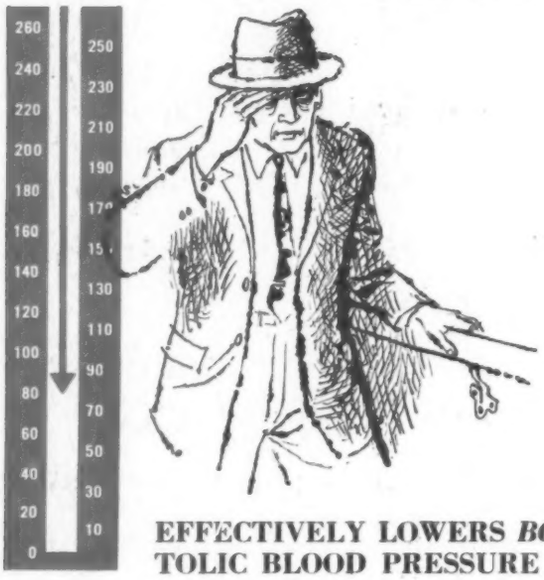

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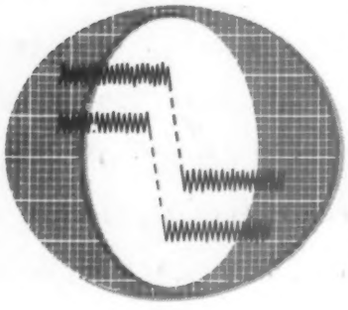

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1. Modell, W.: Am. J. Cardiol. *3*:139 (Feb.) 1959.

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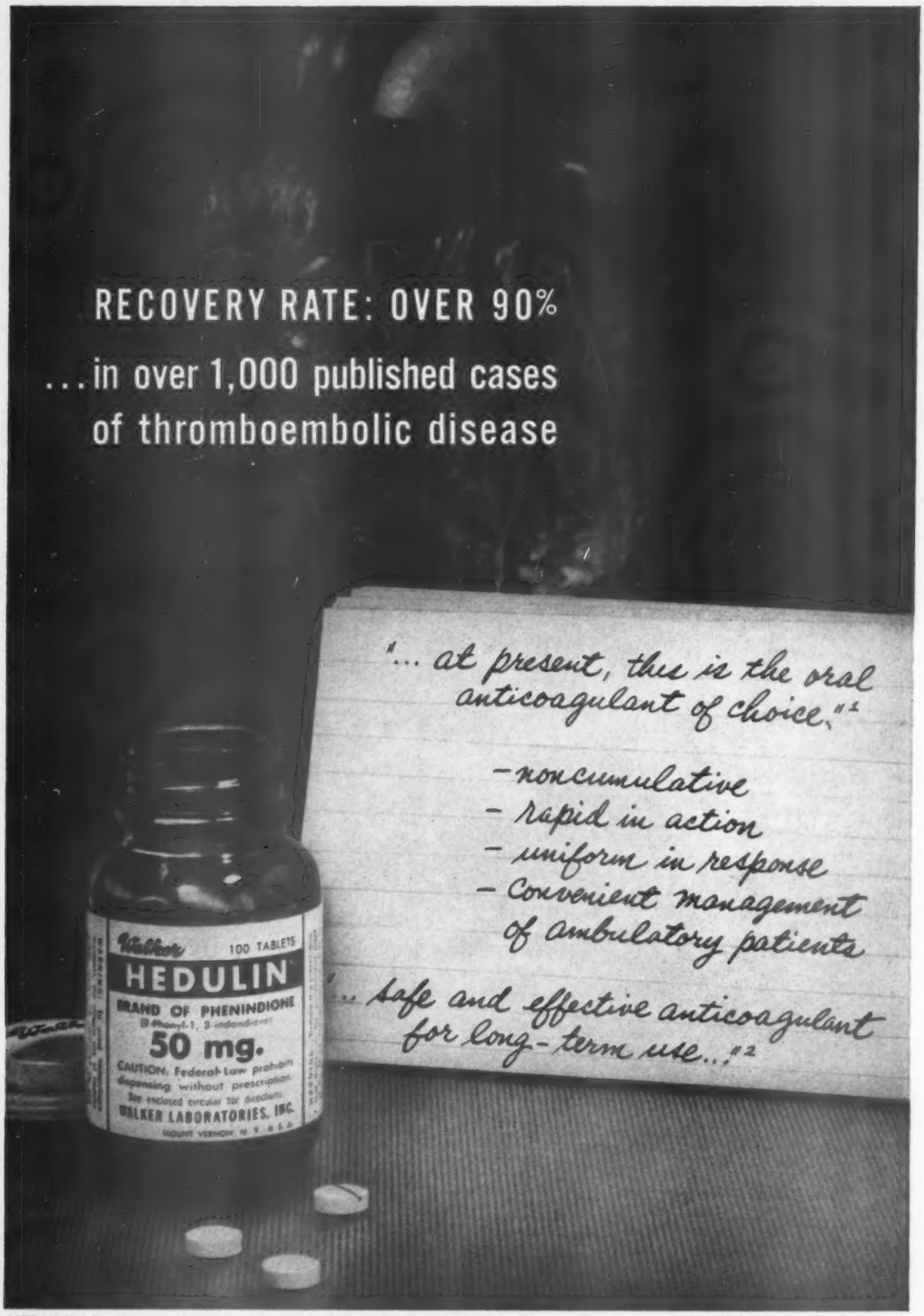

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1. Breneman, G. M., and Priest, E. McC.: Am. Heart J. 50:129 (July) 1955. 2. Tandowsky, R. M.: Am. J. Cardiol. 3:551 (April) 1959.

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1. Biegeleisen, H. I.: Clin. Med. 2:1005, 1955. 2. Roberts, J. T.: Clin. Med. 4:1375, 1957.

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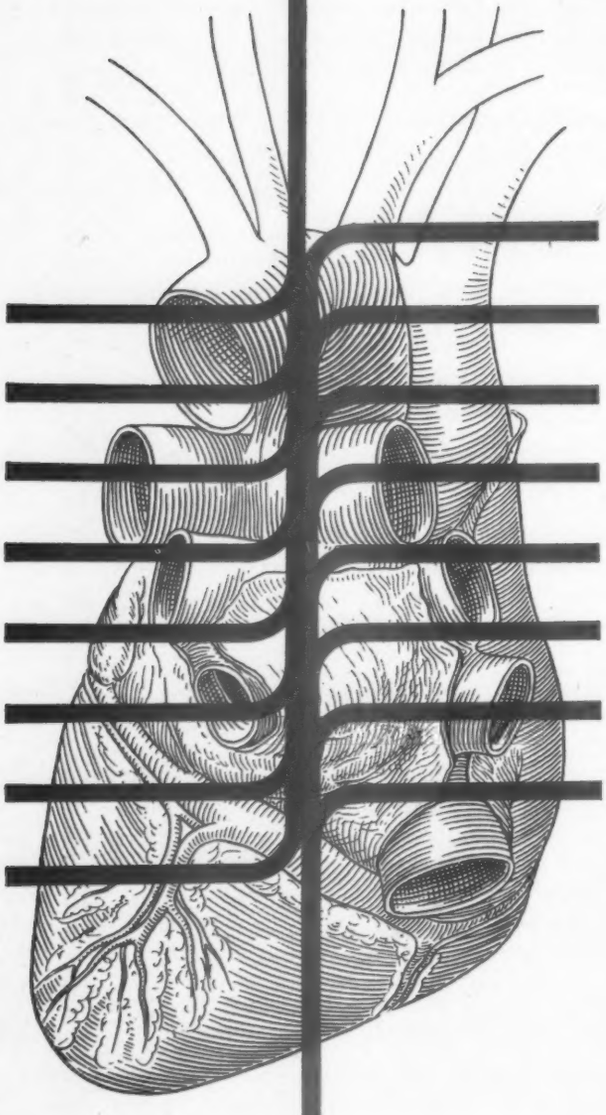
new approach to the concept of "total management" in angina pectoris

new Marplan

a happy balance of potency/safety



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Review

This paper, by the recognized leader of Russian cardiologists, gives a good insight into present-day Soviet investigation and interpretations in the field of hypertension and atherosclerosis. An excellent translator, Dr. W. Raab, to whom we are indebted for this example of contemporary Soviet Russian scientific writing, has attempted to retain the original flavor of the paper which should constitute a major part of its interest for American readers.

Historical Milestones

This historical milestone tells how Piorry introduced the pleximeter in 1828 to improve Auenbrugger's method of percussion.

Special Departments

College Workshop Program

There are still openings in some of the College Workshops announced in the February issue of the Journal, page 289. Registrants write at once to the Executive Director of the American College of Cardiology, Empire State Building, New York 1, New York.

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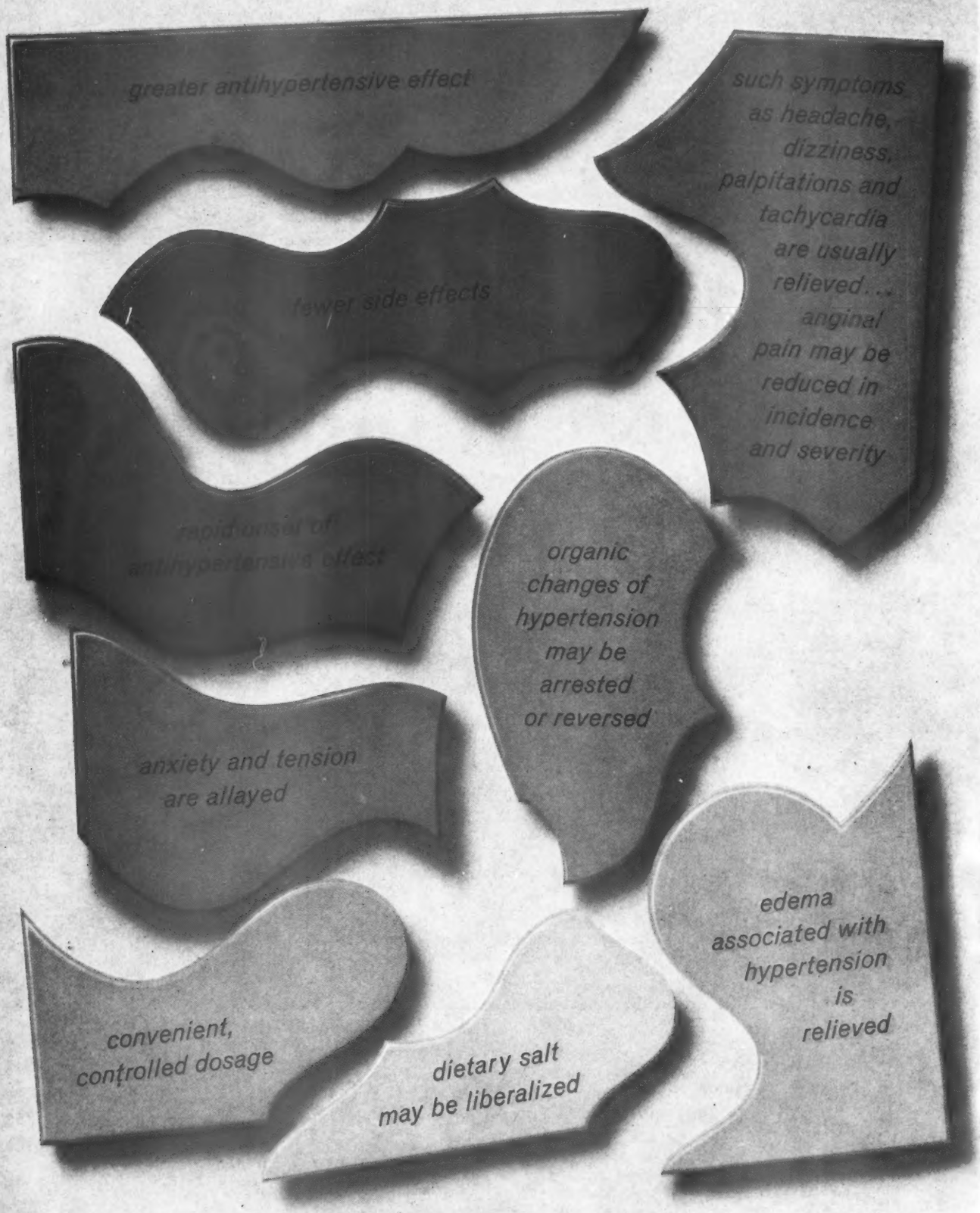

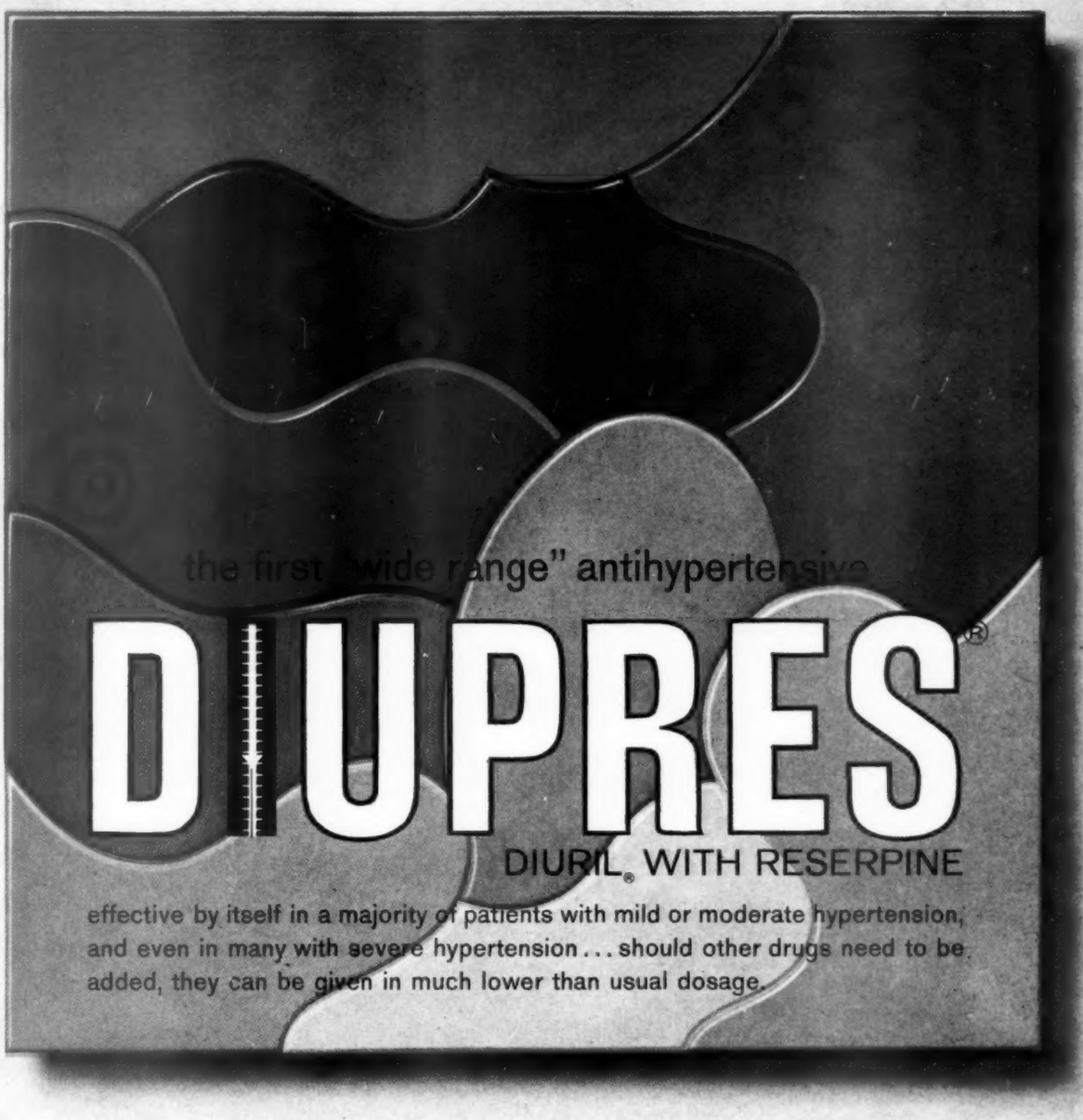

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☐ *Caraway, Wendell T.*—**MICROCHEMICAL METHODS FOR BLOOD ANALYSIS.** Pub. Jan. '60, 128 pp., 7 il., $5.25

☐ *Cruickshank, R.* and *A. A. Glynn*—**RHEUMATIC FEVER:** Epidemiology and Prevention. Pub. Oct. '59, 194 pp., 41 il., $5.50

☐ *Dale, W. Andrew*—**AUTOGENOUS VEIN GRAFTS AND RELATED ASPECTS OF PERIPHERAL ARTERIAL DISEASE.** Pub. Nov. '59, 138 pp., 62 il. (1 in full color), $6.00

☐ *Fleisch, Alfred*—**NEW METHODS OF STUDYING GASEOUS EXCHANGE AND PULMONARY FUNCTION.** Pub. Feb. '60, 132 pp., 33 il., $5.75

☐ *Fleischmajer, Raul*—**THE DYSLIPIDOSES.** Pub. May '60, 528 pp., 184 il., $13.50

☐ *Gould, S. E.*—**PATHOLOGY OF THE HEART** (2nd Ed.). Pub. Dec. '59, 1152 pp. (7 × 10), 977 il. (6 in full color), $32.50

☐ *Greenberg, David M.*, and *Harold A. Harper*—**ENZYMES IN HEALTH AND DISEASE** (26 Distinguished Contributors). Pub. March '60, 472 pp., 177 il., $14.50

☐ *Holland, William C.*, and *Richard L. Klein*—**CHEMISTRY OF HEART FAILURE** (Amer. Lec. Living Chemistry). Pub. date June '60, about 139 pp.

☐ *Hurst, J. Willis*—**CARDIAC RESUSCITATION** (8 Expert Contributors). Pub. Feb. '60, 152 pp., 29 il., $5.50

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☐ *Mackby, M. Judson*—**THE SURGICAL TREATMENT OF PORTAL HYPERTENSION, BLEEDING, ESOPHAGEAL VARICES AND ASCITES** (Amer. Lec. Surgery). Pub. date May '60, about 336 pp. (7 × 10), 49 il. (2 in full color)

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☐ *Myers, J. Arthur*—**DISEASES OF THE CHEST INCLUDING THE HEART** (With Contributions by 84 Authorities). Pub. Nov. '59, 1024 pp. (7½ × 10½), 679 il., $34.50

☐ *Nissen, Rudolf*, and *Roger H. L. Wilson*—**PAGES IN THE HISTORY OF CHEST SURGERY.** Pub. date May '60, about 63 pp.

☐ *Nyboer, Jan*—**ELECTRICAL IMPEDANCE PLETHYSMOGRAPHY:** The Electrical Resistive Measure of the Blood Pulse Volume, Peripheral and Central Blood Flow (Amer. Lec. Medical Physics). Pub. Nov. '59, 264 pp., 104 il., $7.50.

☐ *Schamroth, Leo*, and *Fay Segal*—**AN INTRODUCTION TO CONGENITAL HEART DISEASE.** Pub. date April '60, 126 pp., 86 il., $4.50

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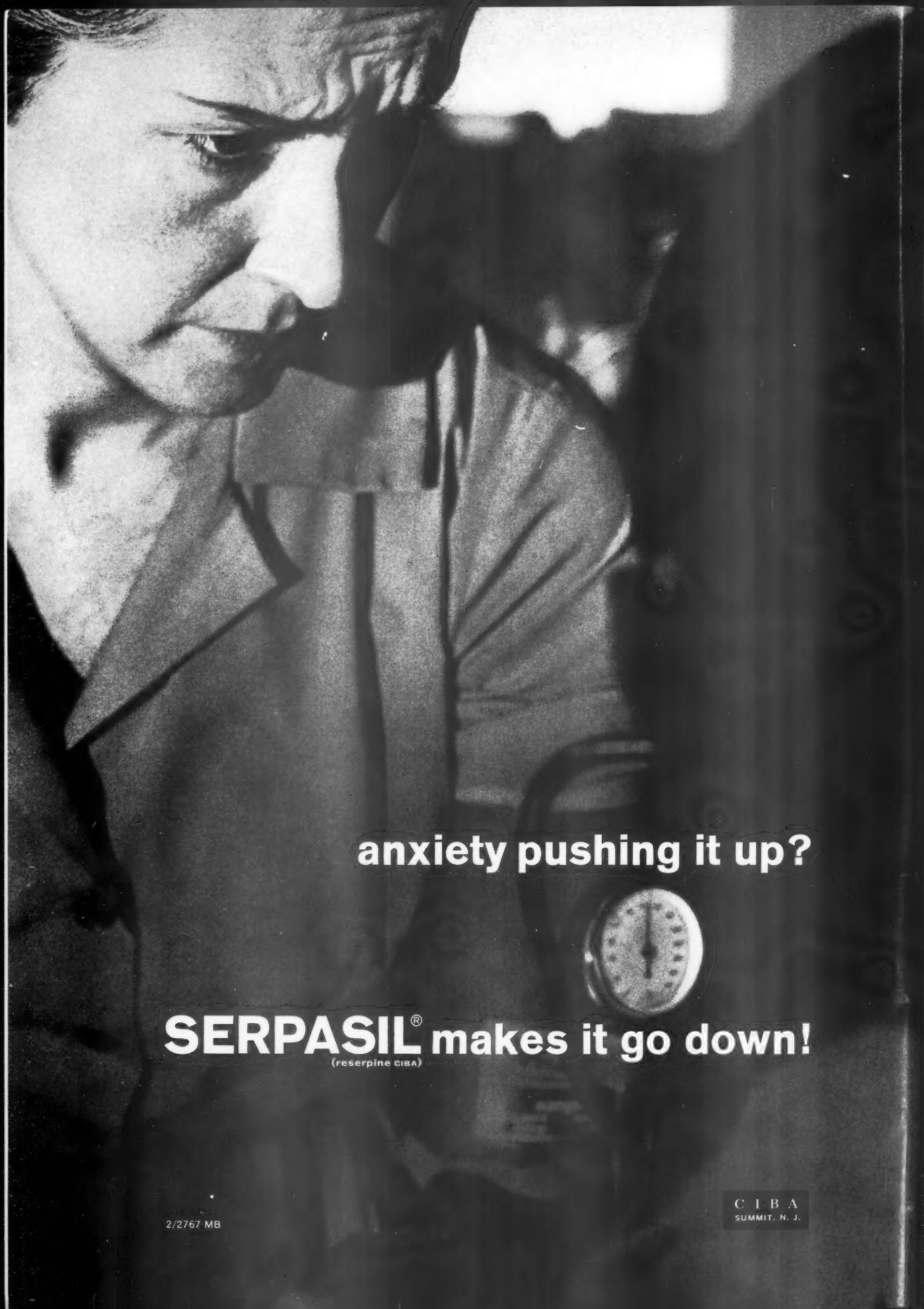
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1. Fremont, R.E.: Personal Communication (Dec., 1959).
2. Summary of Case Reports on File, Ives-Cameron Company.
3. Sherber, D.A.: Personal Communication (Oct., 1959).
4. Russek, H.I.: Personal Communication (Oct., 1959).

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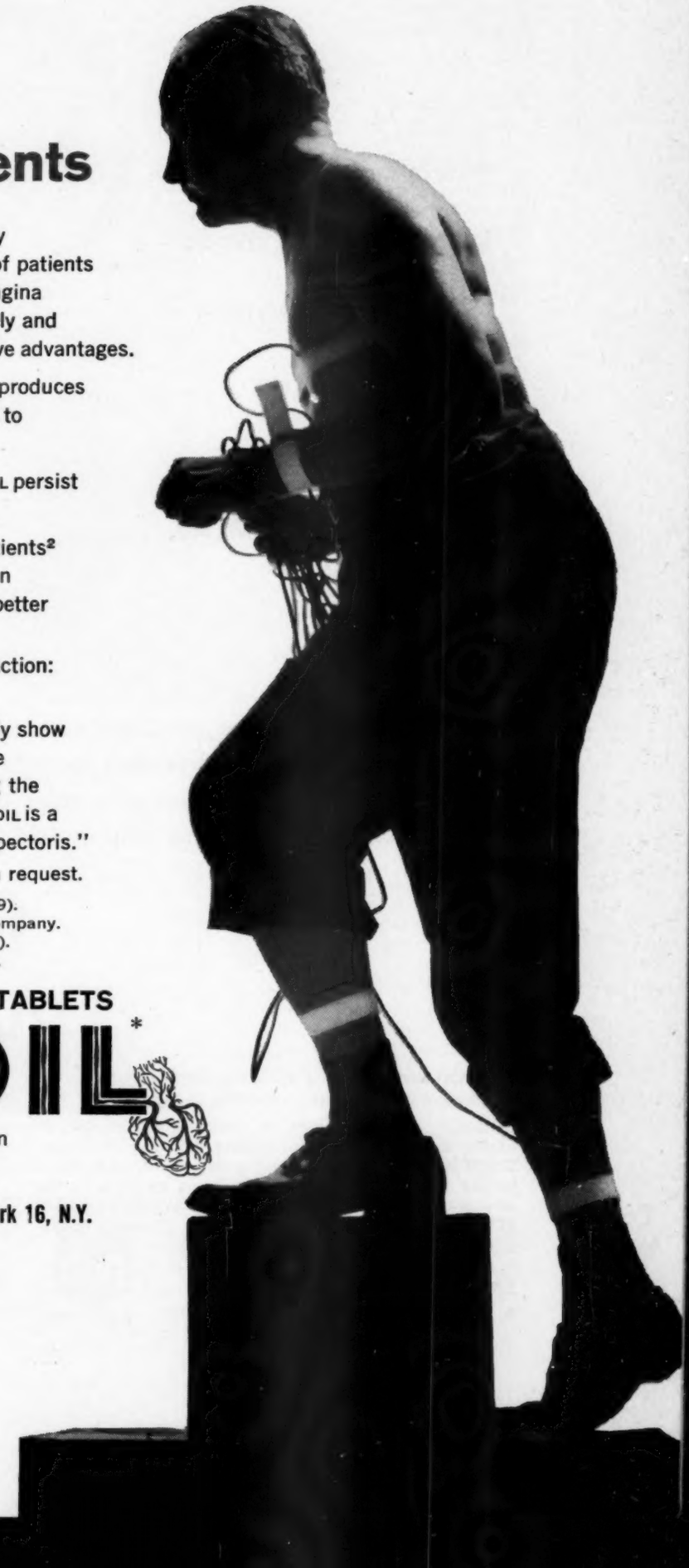

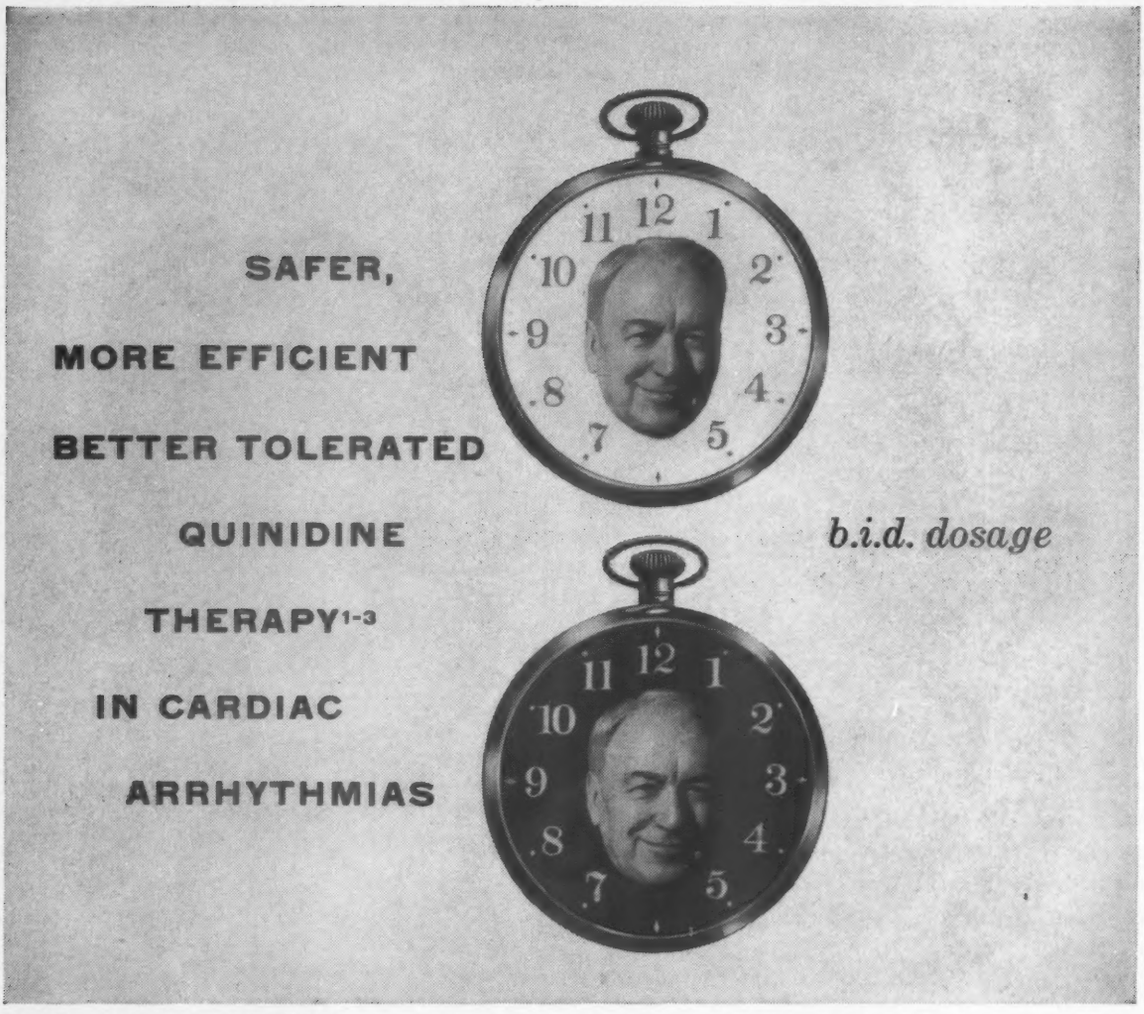

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1. Bellet, S.; Finkelstein, D., and Gilmore H.: A.M.A. Archives Int. Med. 100:750, 1957.
2. Bellet, S.: Amer. Heart J. 56:479, 1958.
3. Finkelstein, D.: Penn. Med. J. 61:1216, 1958.

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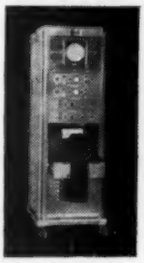

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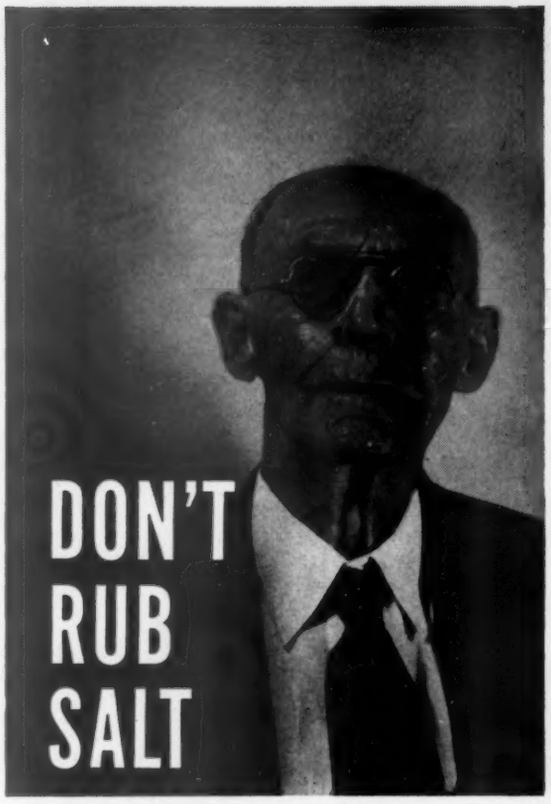

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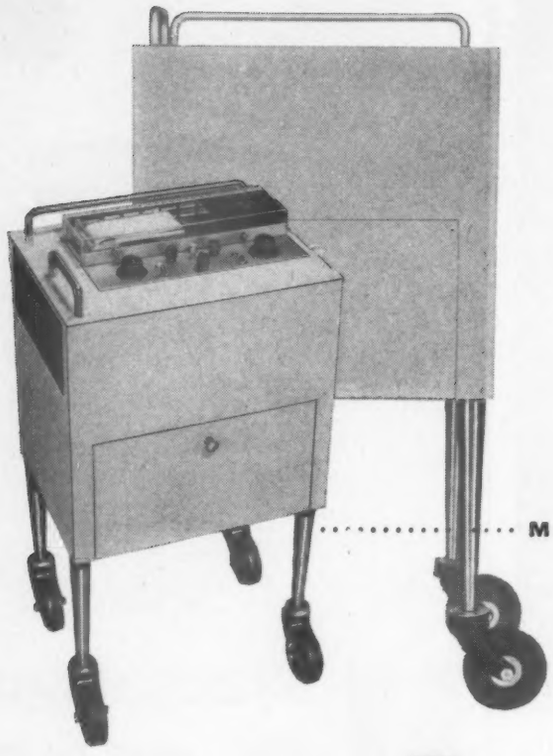

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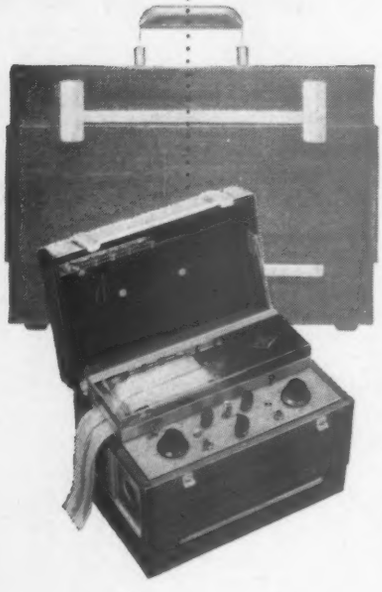

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Source*	Indication	Number of Patients	Results
Moser, K. M., et al.: Circulation 21:337, 1960.	Acute deep thrombophlebitis	62	decreased pain, disability, complications, reduced mortality due to pulmonary embolization—in a controlled study
Singher, H. O., and Chapple, R. V.: Clin. Med. 6:439, 1959.	Pulmonary embolism	33	70% excellent; 24% questionable; 6% poor; "no untoward side effects"
Chapple, R. V., and Singher, H. O.: Canad. M.A.J. 81:231 (Aug. 15) 1959.	Phlebothrombosis	171	65% excellent; 26% good; 9% poor
Howden, G. D.: Canad. M.A.J. 81:382 (Sept. 1) 1959.	Central retinal vein thrombosis	1	"...an excellent thrombolytic response ...remarkable visual improvement"
Carroll, B. J.: Angiology 10:308, 1959.	Phlebothrombosis	82	60 excellent; 19 good; "...a distinct advance in the treatment of thrombophlebitis"
Harloe, J. P.: Angiology 10:283, 1959.	Thrombophlebitis	4	"more rapid resolution...more clear-cut clinical response"
Cliffton, E. E.: Angiology 10:244, 1959.	Peripheral venous thrombosis	38	improvement in large majority
	Pulmonary embolism	5	4 completely relieved
	Retinal vein thrombosis	2	"no further progression"
Moser, K. M.: Angiology 10:319, 1959.	Deep venous thrombosis	41	rapid response if treated within 5 days
Sheffer, A. L., and Israel, H. L.: Angiology 10:292, 1959.	Pulmonary embolism	6	4 excellent; 2 good
	Acute thrombophlebitis	9	good
	Retinal vein thrombosis	7	2 excellent; 5 no benefit
Stewart, C. F.: Angiology 10:299, 1959.	Iliofemoral thrombophlebitis	2	"remarkable" in 1; "considerable improvement" in the other
Evans, J. A., and Smedal, M. I.: Angiology 10:311, 1959.	Postmastectomy thrombophlebitis of arm	10	3 asymptomatic; 5 improved; "offers promise...in this field"

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VOLUME V MAY 1960 NUMBER 5

Symposium on Catecholamines in Cardiovascular Pathology†

Key Position of Catecholamines in Functional and Degenerative Cardiovascular Pathology*

W. RAAB, M.D., F.A.C.C.

Burlington, Vermont

SINCE the discovery of the chemical nature and pharmacodynamic actions of the catecholamines, epinephrine and norepinephrine, which is linked chiefly with the names of Oliver and Schaefer (1895), Takamine (1901), Aldrich (1901) and von Euler (1946), these powerful substances have been the subject of intensive study concerning their formation, metabolism and physiologic significance. However, despite their well known cardiovascular toxicity, consideration of their potential role in the pathogenesis of functional and degenerative cardiovascular diseases remained nearly excluded from clinical reasoning until quite recently. A new era began when the introduction of relatively simple fluorometric methods for the assay of epinephrine and norepinephrine by Weil-Malherbe and others permitted confirmation and amplification of numerous earlier observations made at the University of Vermont during the last twenty years by means of colorimetric and bio-assay determination of total catecholamines as well as of norepinephrine and epinephrine separately in myocardial, vascular, nervous and cerebral tissue[1–3] (Table 1).

For a long time, traditionally mechanistic and teleological thinking in clinical cardiology caused a nearly unshakeable opposition against the thought that biologically formed and essentially "useful" chemical compounds, like the catecholamines, should be fundamentally involved in the development of some of the most common and most fatal cardiovascular diseases. These objections can be countered with the argument that certain dynamic and metabolic properties of the catecholamines are potentiated by various aggravating circumstances to degrees of severe acute or chronic toxicity. Some important effects of norepinephrine and epinephrine, subject to such potentiations, are the following[2,3]:

(1) Intensification of oxygen consumption by myocardial tissue;

(2) Diminution of cardiac energetic efficiency (= percentage-wise conversion of oxidative energy to mechanical work);

(3) Production of local myocardial hypoxia (due to waste of oxygen plus presumable compression of subendocardial coronary vessels by increased intraventricular pressure) resulting in accumulation of lactic acid;

(4) Tendency to favor the development of myocardial hypertrophy and focal degeneration (possibly by way of alterations of intra-extracellular electrolyte transfer);

(5) Vascular constriction and elevation of blood pressure (probably due to effect on vascular transmembrane cationic gradient); and

(6) Tendency to cause hyperplasia of ar-

* From the Cardiovascular Research Unit of the University of Vermont at the DeGoesbriand Memorial Hospital, Burlington, Vermont.

† Presented at the University of Vermont College of Medicine, August 23–26, 1959.

TABLE I
Some Findings Concerning Catecholamines in Cardiovascular Tissue and Blood

Finding	Colorimetry	Bio-assay	Fluorometry
		Heart Muscle	
Increase after injection of catecholamines	Raab,[1] Bloodworth[47]	Raab and Gigee[35]	Axelrod et al.[36]
Increase after stimulation of cardiac sympathetic nerves	Raab,[1] Raab and Humphreys[37]	Raab and Gigee[35]	...
Increase after exercise	Raab[1]	Hökfelt[43]	...
Increase after exposure to cold	Raab[1]	...	...
Increase after injection of acetylcholine	Raab[1]	...	...
Increase in thiamine deficiency	Raab and Supplee[41]	Goodall[39]	...
Increase after infusion of nicotine	...	Raab and Gigee[45]	...
Increase after overdosage of insulin	Raab[1]	Hökfelt[43]	...
Increase in renal insufficiency	Raab,[42] Raab and Gigee[46]	Hökfelt,[43]* Raab and Gigee [6]†	...
Increase after recent myocardial infarction	...	Raab and Gigee[45]*,‡	...
Increase after administration of iproniazid	...	Pekkarinen et al.[10]	Pletscher[21]
Decrease after sympathectomy	Raab and Maes[38]	Goodall,[39] Goodall and Kirshner[40]	...
Decrease after administration of reserpine	...	Paasonen and Krayer,[61] Pekkarinen et al.,[10] Waud et al.[11]	...
Decrease after ganglionic blockade	...	Pekkarinen et al.[10]	...
		Arterial Walls	
Increase after injection of catecholamines	Raab and Gigee[29]	Raab and Gigee,[29] Burn et al.[44]	...
Decrease after administration of reserpine	...	Burn[12]	...
		Blood	
Increase after injection of catecholamines	Raab and Gigee[29]	Raab and Gigee[29]	Watts and Poole[60]
Increase after exercise	Raab[1]	...	Gray and Beetham,[48] Gazes et al.,[16] Lovatt-Evans et al.[52]
Increase after administration of nicotine	...	...	Kiser et al.[49]
Increase after overdosage of insulin	...	Satake[56]	Millar[55]
Increase in renal insufficiency	Raab,[42] Raab et al.[50]	...	Manger,[51] Zileli et al.[62]§
Increase after exercise exaggerated in patients with angina pectoris	Raab[1]	...	Gazes et al.,[16] Starcich and Ambanelli[17]‖
Increase after myocardial infarction	...	...	Gazes et al.,[16] Starcich and Ambanelli[17]
Normal in "essential" hypertension	Raab[54]	...	Goldfien et al.[53]

* Norepinephrine increased, epinephrine normal.
† Total catecholamines and epinephrine increased, norepinephrine diminished.
‡ Total catecholamines normal, epinephrine increased, norepinephrine decreased.
§ Increased with one method, normal with another.
‖ Increased during anginal pain.

terial intima and to accelerate and augment intimal lipid deposition.

Potentially pathogenic intensification of factors 1 to 6 occur (1) if catecholamine formation and discharge is quantitatively exaggerated (examples: pheochromocytoma, emotional overstimulation of sympathetic system); (2) if cardiac catecholamine action is potentiated by an excess of thyroid hormone (example: thyrotoxicosis); (3) if cholinergic and/or sympatho-inhibitory mechanisms are deficient (example: lack of physical exercise[5]); (4) if ischemia-producing coronary vascular damage, arterial hypertension and/or excess adrenal

corticoids sensitize the heart muscle to the hypoxiating and necrotizing effects of the catecholamines (example: coronary sclerotic and cortisol + stress-induced myocardial hyalinization, necrotization and fibrosis[6–9]); and (5) if exaggerated mineralocorticoid action sensitizes the arterial walls to the constrictor effect of the catecholamines (examples: hypertension in the presence of adrenal cortical tumors, toxemia of pregnancy[4]).

Effective therapeutic procedures are directed against these catecholamine-toxifying mechanisms: sympathectomy and ganglionic blockers (possibly also certain amine oxidase inhibitors) eliminate or reduce discharges of norepinephrine at the sympathetic nerve terminals.[3,10] Rauwolfia drugs deplete the cardiovascular catecholamine stores through facilitation of their enzymatic destruction.[11,12] Roentgen radiation of the adrenal glands diminishes adrenal medullary discharges of epinephrine.[2,3] (The so-called "adrenolytic" drugs, such as dibenamine and Regitine,® counteract circulating catecholamines but fail to reduce or inhibit those present in the myocardium.[3]) Thyrostatic treatments impair functional effectiveness of the cardiac catecholamines.[3,13] Sodium withdrawal and natriuretic drugs reduce vascular responsiveness to vasoconstrictor catecholamine action.[4,14,15] Vagal stimulation (e.g., carotid sinus compression), digitalis and the development of a high vagal and/or sympatho-inhibitory[59] tone counteract myocardial oxygen wastage and improve cardiac efficiency.[3]

Role of Catecholamines in Various Cardiovascular Diseases

With the principles just outlined in mind, it is possible to interpret the pathogenic background and therapeutic responses of various functional and degenerative cardiovascular diseases more satisfactorily than by the customary mechanistic concepts alone, notwithstanding due recognition of the great significance of certain contributory mechanical factors, such as reduced coronary flow and increased peripheral resistance.

Angina Pectoris: In patients with angina pectoris, the discharge of catecholamines into the circulation during exercise and pain is usually exaggerated.[2,3,16,17] The heart muscle avidly absorbs and accumulates locally liberated as well as circulating catecholamines.[1,35,36,47,63]

Acute influxes of sympathogenic norepinephrine and/or adrenal medullary epinephrine into the myocardium (e.g., during effort, emotional excitement, tobacco smoking, overdosage of insulin) intensify cardiac oxygen consumption. Accordingly, in the presence of coronary sclerosis, the coronary venous oxygen content falls sharply during effort and anginal pain, and there is evidence of myocardial anaerobic glycolysis,[19] consistent with acute oxygen-wasting catecholamine action without adequate coronary dilatation. The resulting myocardial hypoxia is believed to elicit pain through local accumulation of unoxidized lactic acid.[2]

Contrary to time honored but unproved beliefs, Gorlin[19] found that nitroglycerin does not improve the "fixed" inadequate coronary flow in patients with angina. Since, on the other hand, nitroglycerin is capable of abolishing the catecholamine-induced depression of the T wave,[3] it seems possible that the nitrites interfere at some as yet undetermined level of myocardial metabolism (possibly by affecting the exchange of electrolytes[20]).

All effective forms of long range treatment for angina pectoris (except surgical revascularization) are based on direct or indirect anti-catecholamine action[2,3]: reduction of sympathetic stimuli through physical and emotional relaxation, cervicothoracic sympathectomy, ganglionic blockade, and roentgen radiation of the overexcitable adrenal medulla reduce or eliminate catecholamine discharges. Thyrostatic procedures (thyroidectomy, thiourea compounds, radioiodine) diminish metabolic hypoxiating catecholamine effectiveness. Iproniazid and related drugs exert, aside from amine oxidase inhibition, certain still unexplained antiadrenergic effects (blockade of catecholamine liberation?[21]). Cholinergic, sympatho-inhibitory action through digital compression of the carotid sinus can be utilized during individual attacks of angina pectoris.[2,3]

Myocardial Degeneration and Necrosis Without Vascular Occlusion: Clinical features, including electrocardiograms, suggestive of myocardial infarction, and disseminated hyaline, necrotic and fibrotic foci, especially in the subendocardial layers, yet without evidence of significant vascular pathology, have often been reported.[2] Such events can be attributed to sympathetic "storms" (e.g., in cases of pheochromocytoma) and, possibly, to conditioning of the myocardium to catecholamine-induced structural injury through adrenal corticoid overaction[6] or high molecular substances.[57] Severe myocardial necroses have been demonstrated under

the combined influence of corticoids or polysaccharides and artificially administered or presumably spontaneously stress-discharged catecholamines.[6–9,57] Such necroses can be prevented by administration of potassium and magnesium salts,[6,57] and by rauwolfia drugs and ganglionic blocking agents which reduce the myocardial catecholamine stores.[9]

Extensive myocardial lesions have also been observed in animals and human beings after prolonged infusion of norepinephrine.[22,23,58]

Postinfarction Syndrome: The findings of increased amounts of catecholamines in blood[16] and urine,[3] and of an augmented epinephrine concentration in the intact heart muscle[3] after myocardial infarction, as well as the partial prevention of postinfarction tachycardias and arrhythmias by antiadrenergic and antithyroid drugs,[3] suggest a possible involvement of catecholamine overaction in the cardiac postinfarction complications.

The therapeutic usefulness of norepinephrine in postinfarction hypotension is based, in part, on baroceptor-induced vagal counterreflexes which overcompensate the specific adrenergic effects of moderate norepinephrine doses on the heart.

Congestive Heart Failure: Acute failure of the left ventricle with pulmonary congestion and edema occurs after injection of large doses of epinephrine and in cases of pheochromocytoma. It is unlikely that catecholamine overactivity *per se*, unless excessive, can throw an otherwise normal heart directly into failure but a chronic, insidiously injurious influence of catecholamines upon myocardial metabolism and structure may ultimately create a state of abnormal functional vulnerability. Coincidence with other contributing metabolic or dynamic factors (corticoid overactivity, thyrotoxicosis, deterioration of sympatho-inhibitory and cholinergic mechanisms, coronary sclerosis, cardiac hypertrophy, myocarditis, valvular lesions) can probably suffice to make even the physiologically increased influx of catecholamines during effort, emotional excitement, etc., hazardous. Reports regarding the catecholamine concentration in failing human hearts are contradictory.[46,47]

Significantly, the metabolic characteristics of the human heart in failure (decreased efficiency, diminution of energy-rich phosphates and of glycogen) closely resemble those elicited by toxic catecholamine action on the myocardium.[1–3]

Ganglionic blockade, sympatho-inhibitory and vagal stimulation by carotid sinus compression and vagotropic morphine prove often dramatically effective in acute pulmonary congestion.[3] Chronic congestive failure is sometimes alleviated by sympathectomy[24] or thryostatic procedures.[3] The efficiency-increasing effect of digitalis glycosides contrasts with efficiency-impairing catecholamine action.

Thus, it may be assumed that exaggerated catecholamine activity, in combination with other aggravating circumstances, can serve both as a slowly conditioning and as an acutely triggering contributory factor in the development of congestive heart failure.

Thiamine Deficiency and Beriberi Heart: In thiamine deficiency, the myocardial catecholamine concentration is increased.[2,3] Cardiovascular dynamic anomalies (augmented cardiac output and pulse pressure, decreased peripheral resistance) and the electrocardiogram (S-T and T changes) are analogous to those elicited by epinephrine. Sensitivity to epinephrine is greatly accentuated and congestive heart failure develops terminally. Administration of thiamine restores the cardiac catecholamine concentration promptly to normal and is therapeutically more effective than digitalis.[3]

Thyrotoxic and Hypothyroid Heart: In accordance with the catecholamine-potentiating action of the thyroid hormone,[13] an exaggerated activity of the latter is accompanied by cardiac acceleration, increased cardiac output and oxygen consumption, decreased efficiency, bouts of auricular fibrillation and, in cases of long standing, "hypoxic" changes in the electrocardiogram and ultimate congestive failure.[2] Catecholamine-inhibiting thyrostatic therapy is more effective than digitalis. Coronary sclerosis occurs relatively rarely, probably due to the serum cholesterol-depressant action of the thyroid hormone.

In myxedema, inactivation of the catecholamines causes bradycardia. Severe hypercholesterolemic coronary atherosclerosis may permit the appearance of anginal symptoms despite low catecholamine activity.[2]

The Heart in Uremia: Advanced renal excretory insufficiency with uremia is associated with a rise in the total serum catecholamine concentration[25,51] possibly due to renal retention of epinephrine, norepinephrine and some of their immediate derivatives. This seems to explain, at least in part, the "false positive" Regitine

tests for pheochromocytoma in patients with uremia, and certain cardiac complications, such as the common depression of S-T and T, and ultimate congestive failure with a proneness toward pulmonary edema. The electrocardiographic changes are often temporarily abolished by Regitine and in some patients with uremia the heart muscle was found postmortem to contain an abnormally high concentration of total catecholamines.[2,3] In others this was not the case,[47] possibly due to already established structural alterations of the myocardium.[2]

"Hypertensive" Heart Disease: The old conconcept of so-called "hypertensive" heart disease (left ventricular hypertrophy, "strain" pattern and final failure), as being caused primarily and solely by the mechanical "burden" of increased peripheral resistance, is untenable in view of the lack of a regular relationship to height and duration of hypertension, and the not infrequently divergent behavior of blood pressure and heart function under treatment. For instance, after sympathectomy, the cardiac manifestations may revert to normal or near normal despite unchanged or even further increased blood pressure levels.[2] Here too, the metabolic influences of overactive, catecholamine-discharging sympathetic neurones, supplying the blood vessels and heart separately and in varying distributions, must not be disregarded. Mineralocorticoid overaction can be assumed to contribute in some instances.[4]

"Loafer's" Heart: There is reason to believe that the well known high vagal and/or sympatho-inhibitory[59] tone of endurance athletes is more specifically representative of the original biologic species Homo sapiens than the cardiac characteristics which have developed in our age of nearly complete replacement of physical effort by mechanical devices. The high sympathetic tone of our contemporary "normal" Western hearts, even at rest (faster rate, shorter isometric tension period[5]), can be regarded as an artifact induced by civilization, favoring a permanently accentuated catecholamine activity with all of its potentially pathogenic implications.[5,26]

Correlated electrocardiographic and electroencephalographic studies of Letunov[64] suggest that the training-induced shift of central stimulus formation toward the vagal and sympatho-inhibitory pattern is mediated by the cerebral cortex. This seems to distinguish the long range effect of acute sympathetic stimulations during exercise from those occurring in connection with hypothalamic emotional excitements. The latter do not contribute to an elevation of the vagal and sympatho-inhibitory tone at rest.

Socioeconomic pressures, anxieties and frustrations contribute further to exaggerated centrogenic stimulations of the catecholamine-discharging sympathetic system, and additional catecholamine bombardments of the heart are elicited by the abuse of nicotine.[27]

The sympathicotonia of the physically inactive "loafer's" heart is reversible by vigorous and persistent exercise[5] but there exists little hope that this old-fashioned and inconvenient method for protection of the heart will be widely resumed. The high incidence of myocardial fibrous degeneration and death from coronary disease among the sedentary population groups in Western countries[5] is likely to rise further with further increasing physical immobilization and with the growing complexity and diminishing purposefulness of our "supercivilized" daily life.

Atherosclerosis: Present-day preoccupation with the role of dietary fat and lipids in atherogenesis has diverted attention from those factors which predispose the arterial intima to the deposition of lipids. It is possible that exaggerated catecholamine action which promotes intimal hyperplasia and which causes an accelerated and intensified deposition of lipids in arterial walls[28] may be involved also in the process of atherogenesis.

Like the heart muscle (and in striking contrast to the striated muscles), the vascular walls avidly absorb and accumulate circulating catecholamines.[29] Central nervous sedation seems to exert an antiatherogenic, and central nervous stimulation an atherogenesis-promoting effect.[30] This field of neurogenic influences in atherogenesis is particularly in need of further thorough investigation.

Pheochromocytomatous Hypertension: Paroxysmal or sustained elevations of the blood pressure are evoked by temporary or continuous catecholamine discharges, respectively, from the tumor tissue. Diastolic pressure level and heart rate vary according to the prevalence of either norepinephrine (high diastolic pressure, reflectory vagal bradycardia) or epinephrine (low diastolic pressure, tachycardia).

Early excision of the tumor reverts all pathologic manifestations to normal, including renal and ocular vascular damage, anginal symptoms, etc. Otherwise, severe general cardiovascular disease may become permanent.[2]

"Neurogenic" Hypertension: A primarily

neurogenic sympathicotonic and, thus, catecholamine-mediated origin of acute or subacute arterial pressure elevations appears obvious in cases of cerebral injury, infection or tumor. Arteriolar sclerotic ischemia of certain areas of the brain and medulla oblongata seems likewise to elicit centrogenic vasoconstrictions in the periphery.[4]

Arteriosclerotic loss of distensibility of vascular pressoreceptor areas (carotid sinus and others) inactivates vagal and sympatho-inhibitor depressor reflexes and, thus, creates a functional sympathetic vasoconstrictor preponderance.[4]

Participation of central neurogenic emotional factors in the origin of "essential" hypertension is emphatically stressed by the Russian school.[31] Reports on blood catecholamine levels and urinary catecholamine excretion do not provide any impressively abnormal findings[4,51] but this does not necessarily rule out an intensified intravascular catecholamine action and turnover.[51]

Functional signs of exaggerated vasopressor catecholamine activity in "essential" hypertension are: (1) the analogy of clinical and norepinephrine-induced elevation of the diastolic pressure; (2) aggravation by sympathetic stimulating emotional stresses; and (3) frequent depressor effectiveness of sympathectomy, ganglionic blockade, catecholamine-depleting rauwolfia drugs, central sedatives and spinal anesthesia.[2,4]

"Hormonal" Hypertension: An abnormally augmented mineralocorticoid activity in Cushing's syndrome, primary aldosteronism and, probably, toxemia of pregnancy,[32] serves as a "conditioning" factor in the development of hypertension. The mineralocorticoids (probably by decreasing the transmembrane sodium gradient of the vascular cells[4]) sensitize the arterial walls to the constrictor action of their norepinephrine supplies which, in turn, reduce the intra-extracellular potassium gradient.[4] Thus, both corticoids as vascular sensitizers, and catecholamines as vascular stimulators, contribute jointly to intense vasoconstriction by altering cellular electrolyte balance.

Reduction of available sodium (dietary sodium restriction, administration of chlorothiazide, adrenalectomy) eliminates the catecholamine-potentiating element and reduces the blood pressure even in "essential" hypertension, in which the adrenal cortex seems to play a merely "permissive" rather than a "conditioning" role.

"Renal" Hypertension: The catecholamines contribute to the development of "renal" hypertension only insofar as they are capable of producing severe renal vasoconstriction[2] (e.g., in cases of pheochromocytoma) with resulting ischemia and secondary liberation of nephrogenic pressor material. In established nephritic or nephrosclerotic hypertension, renally retained circulating catecholamines may contribute to the maintenance of high blood pressure levels.[4,51] Antiadrenergic therapy is sometimes partially effective.

Neurogenic and Hormonal Hypotension; Shock: An abrupt deprivation of the catecholamine supply of the vascular system (sympathectomy, ganglionic blockade), and central disturbances of the sympathetic nervous outflow (encephalitis, tabes dorsalis, etc.) are often accompanied by postural hypotension and syncope.[33]

Similar events occur when primary or secondary adrenal cortical insufficiency (Addison's disease, adrenalectomy, infections, hypopituitarism) seem to impair vascular reactivity to the intrinsic catecholamine supplies of the arterial walls. In addition, a diminished catecholamine excretion in the urine has been observed in some instances of postural hypotension.[33]

The most serious forms of hypotension occur in cardiogenic, traumatic, infectious and other types of shock. Infused norepinephrine sometimes succeeds in restoring normal or near normal blood pressure levels but the vascular responsiveness is often so completely abolished that all pressor agents fail to take effect.

Venous Reactions: Little attention has been paid in the past to the active role of the veins in pathologic cardiovascular dynamics. However, the presence of relatively large catecholamine concentrations in venous tissue[29] and the response of the veins to both centrally elicited and locally produced catecholamine action[34] seems to make future research in this area highly promising.

Summary

The catecholamines, norepinephrine and epinephrine, occupy a prominent position in the dynamic, metabolic and structural pathogenic mechanisms of the most common functional and degenerative cardiovascular disorders, such as angina pectoris, myocardial degeneration and failure, arterial hypertension and atherogenesis. Although they are essential constituents of physiologic cardiovascular regu-

lation, their potentially oxygen-wasting, efficiency-impairing, hypoxiating, necrotizing and vasoconstrictor properties become greatly accentuated by certain abnormal circumstances, such as: (1) excessive formation, liberation and local accumulation of catecholamines in cardiovascular tissues; (2) deterioration of sympatho-inhibitory and cholinergic counter-regulatory mechanisms; and (3) coexisting overactivity of other hormones (adrenal corticoids, thyroid hormone) which potentiate the injurious metabolic effects of the catecholamines on heart and blood vessels, in part possibly by way of derangements of the transmembrane cationic gradient.

Many effective therapeutic measures are based on quantitative diminution and/or appropriate functional inactivation of the catecholamines.

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Certain Aspects of the Role of Catecholamines in Circulatory Regulation*

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WE WERE welcomed to this Symposium by Dr. Raab as a group of what he referred to as "catecholaminiacs." I presume he meant by this that we communally share a vigorous enthusiasm for the belief that the continued study of these substances will unroof helpful areas of knowledge. One might even venture to say that we are composed of two wings: the "good catecholaminiacs" and the "evil catecholaminiacs." The "good" wing holds that the physiologic activity of these substances is an essential ingredient of a fully competent organism and that, occasionally, when the circulation of the organism deteriorates markedly, the catecholamines are called upon to perform such a Herculean task that the very intensity of their action may unwittingly produce a harmful result. On the other hand, the protagonists of the "evil" camp hold that we would, in general, fare better without these widely enthusiastic chemical mediators and that much of the circulatory symptomatology and disease we encounter are attributable to their influence. Not without some reservations, I belong in the former camp.

The purpose of this presentation is to introduce recent evidence concerning the importance of catecholamines in certain aspects of circulatory regulation. More specifically, the data my colleagues and I have gathered relate to the regulation of the contraction of the ventricle and the external work produced by it. In the following discussion it will be assumed that the reader accepts the view that the stimulation of sympathetic nerves produces the local elaboration of catecholamines, presumably norepinephrine, in the effector organ and that the hemodynamic phenomena observed as the result of such stimulation are attributable to its action.

REGULATION OF VENTRICULAR CONTRACTION

The basic influence determining the force of contraction of muscle is its length prior to contraction. This accounts for the shape of the curve relating filling pressure to the external work produced by the ventricle of the isolated heart. Such a curve, termed a ventricular function curve,[1] is another way of expressing the basic Frank-Starling relationship.[2,3] A matter of primary concern is the manner in which the central nervous system can alter the position of this curve. Figure 1 shows a schematic résumé of the possible effects that autonomic nerve stimulation can have on ventricular function. The experimental data on which these curves are based has been presented elsewhere.[4–8]

Effects of Autonomic Nerve Stimulation: When the stellate ganglion (to which the rami have been cut) is stimulated, the ventricle will produce a greatly augmented stroke work from any given mean atrial pressure and also from any given left ventricular end diastolic pressure (Fig. 1A). When the distal cut end of either vagus nerve is stimulated, the ventricle will produce appreciably less work from any given mean left atrial pressure. The contractility of the ventricle itself is, however, apparently unmodified by vagal stimulation since, from any given end diastolic pressure, the ventricle will still produce as much external work (Fig. 1B). These findings on vagal stimulation are in accord with the inability of histologists to demonstrate vagal innervation in the ventricular myocardium.

Relation Between Ventricular Pressure and Changes in Myocardial Fiber Length as a Result of Either Sympathetic or Vagal Nerve Stimulation: To study this question a low mass, low inertia instrument

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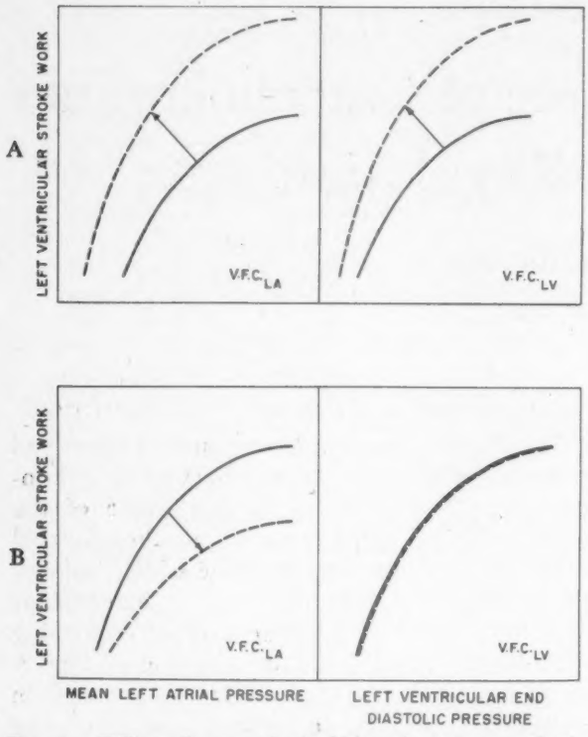

FIG. 1. Effect of sympathetic (A) and parasympathetic (B) cardiac nerve stimulation on the relation between mean left atrial pressure and left ventricular stroke work ($V.F.C._{LA}$) and relation between left ventricular end diastolic pressure and left ventricular stroke work ($V.F.C._{LV}$).

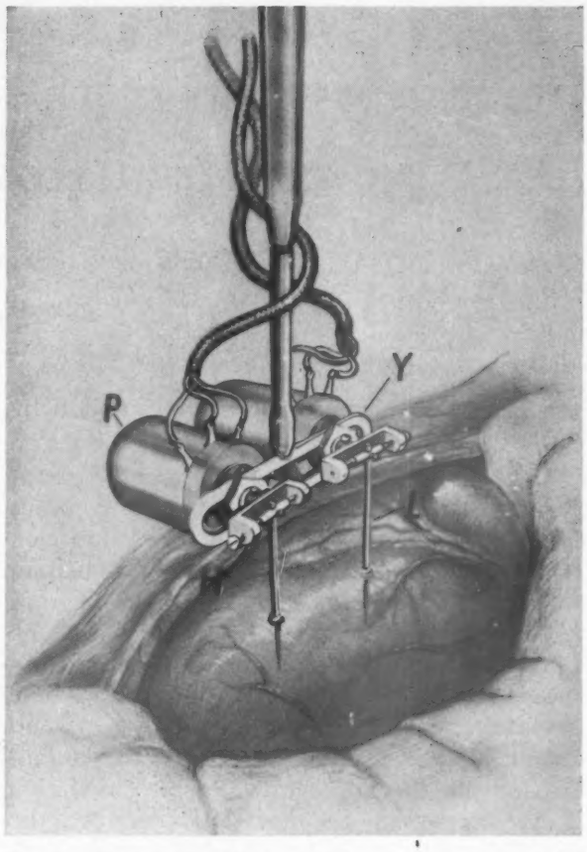

FIG. 2. Instrument for the continuous measurement of changes in the length of a selected segment of left ventricular myocardium. See also Figures 6, 7 and 8 (M.S.L.).

has been devised[4] by means of which it is possible to record the changes in length of a selected segment of myocardium (Fig. 2). With it, one can relate any given change in ventricular diastolic pressure to a simultaneously observed change in myocardial segment length; by infusing and removing blood, the full range of this relationship between pressure and length can be examined. Such curves, diastolic pressure-length curves, are shown in Figure 3. It is noted that at the lower ventricular diastolic pressures a small pressure increment will produce a large augmentation of fiber length while at the higher pressures, the increase in fiber length for any given diastolic pressure increase is small. Further, Figure 3 also shows that during sympathetic stimulation (A) the pressure-length curve is unaltered. The same results, i.e., no change, were obtained during vagal stimulation (B).

The salient implication of these data is that, when the ventricle contracts more forcefully from any given end diastolic pressure as the result of the influence of locally elaborated catecholamines, this does not, or at least need not, involve any change in either the extensibility of ventricular myocardium or the ventricular pressure-length curve. One important consideration must, however, be inserted here. If the heart rate is excessively high (especially if stroke volume is also high or if the heart is failing), then sympathetic stimulation can restore the normal diastolic pressure-length curve by shortening systole and allowing more adequate time for ventricular relaxation to occur.[5]

On the basis of the aforementioned data, one may conclude that the central nervous system can manipulate not only the basic curve relating filling pressure to stroke work but also can shift the curve relating fiber length to the stroke work produced by the ventricle.

The acutely induced changes following stimulation of the left stellate ganglion are shown in Figure 4A. Such stimulation, while the heart was paced at a constant rate produced a substantial rise in aortic pressure, cardiac output (not shown) and calculated ventricular stroke work while filling pressure fell

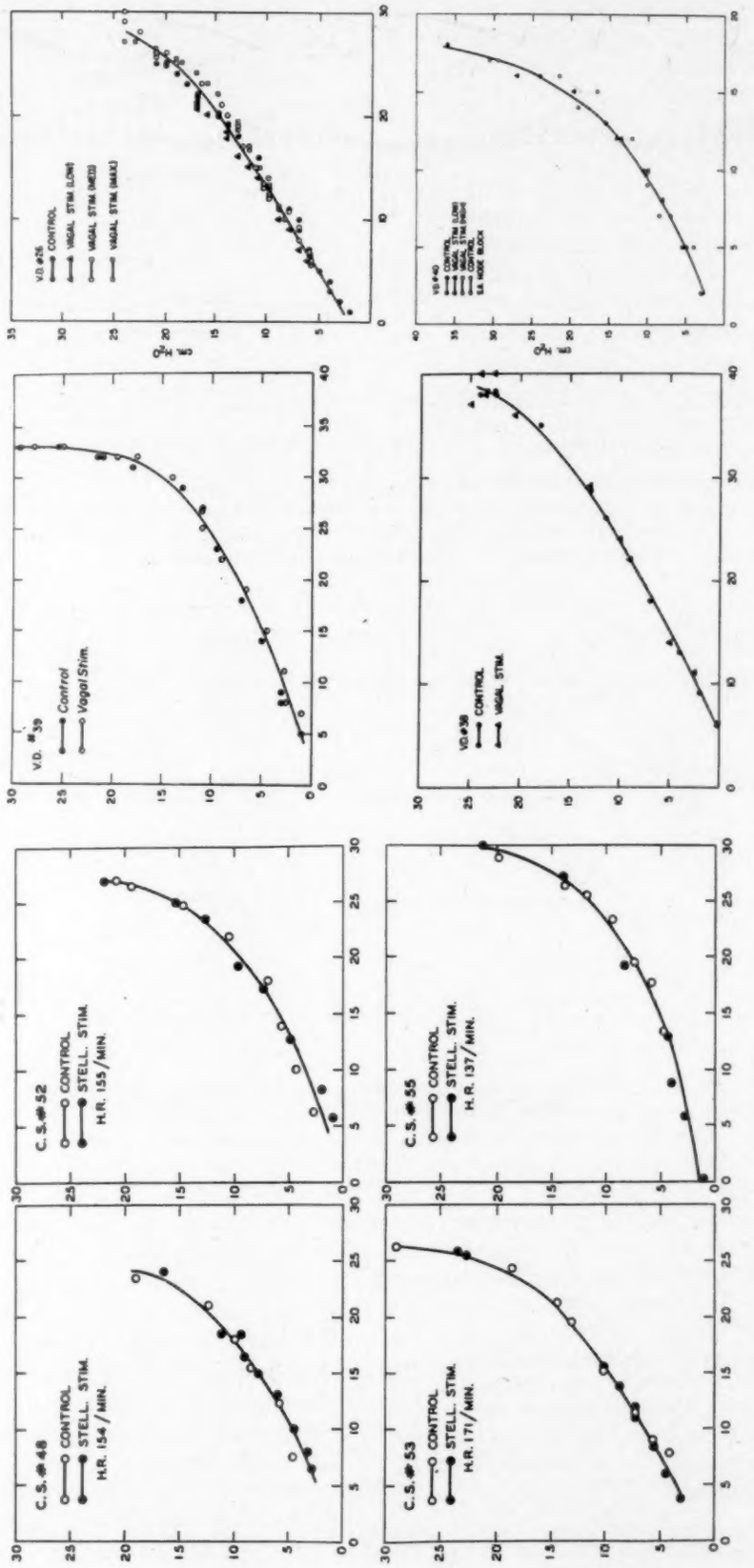

FIG. 3. Effect of left stellate ganglion stimulation (A) and of vagus nerve stimulation (B) on the relation between ventricular diastolic pressure and changes in myocardial segment length (pressure-length curve). All ordinates: pressure in cm. H_2O. All abscissas: changes of fiber length plotted as mm deflection on recorder. Sensitivity of the system was usually such that a 6 to 8 mm. recorder deflection was caused by a 1 mm. change in segment length.

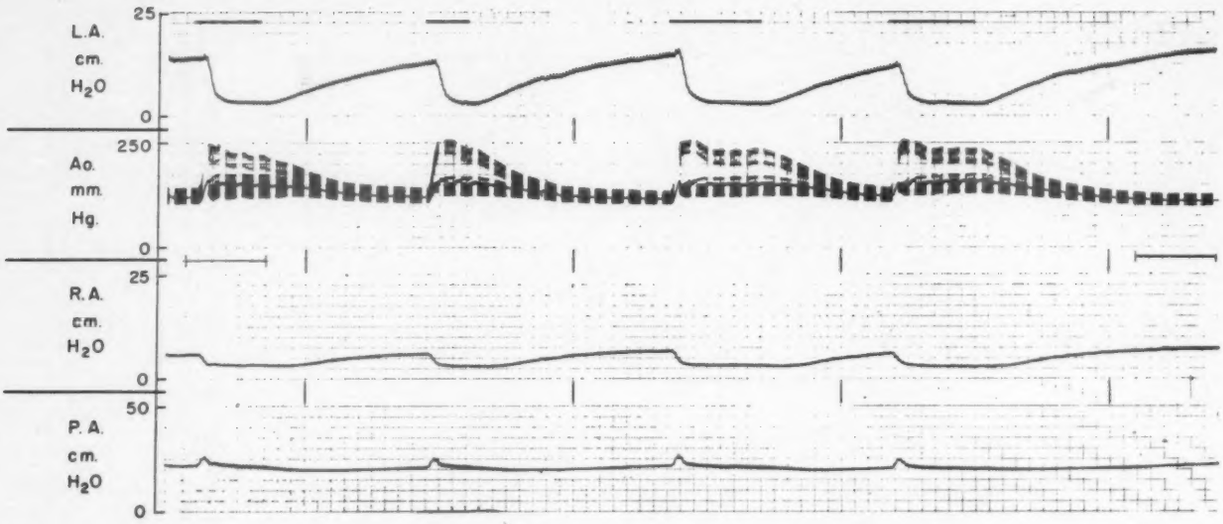

FIG. 4A. Bilateral cervical vagotomy and constant heart rate. In this figure and in Figures 5A, 5B, 6A, 7, 8, 9A and 9B L.A. = mean left atrial pressure; Ao = aortic pressure (full pulse pressure alternating with electrically integrated mean pressure); R.A. = mean right atrial pressure; P.A. = mean pulmonary artery pressure. Bars at the top signal intervals during which the decentralized left stellate ganglion was stimulated.

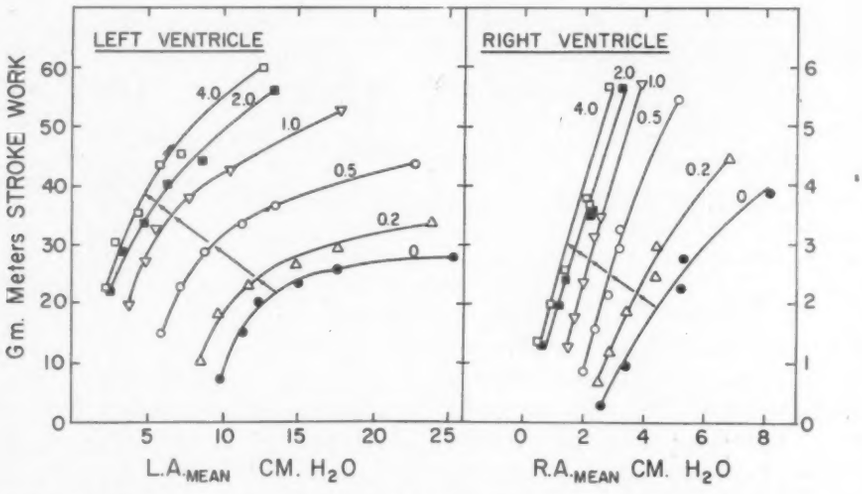

FIG. 4B. Bilateral cervical vagotomy and constant heart rate. Curves relating mean left and right atrial pressure to the stroke work of the left and right ventricle before (0) and during stimulation of the left stellate ganglion at frequencies of 0.2, 0.5, 1.0, 2.0 and 4.0 per second.

markedly. A systematic study of these phenomena resulted in the data shown in Figure 4B, a series of curves for the right and left ventricle relating filling pressure to stroke work. The number adjacent to each curve indicates the impulse frequency (0, 0.2, 0.5, 1.0, 2.0, 4.0) applied to the stellate ganglion. These data assure us that the central nervous system has available pathways with which it cannot only manipulate the position of these curves but can do so systematically by varying the number of impulses it sends down the cardiac sympathetics.

Effect of Carotid Sinus Stimulation and Pressure: The question now arises as to whether the responses which we can elicit by direct autonomic nerve stimulation can also be reflexly evoked. Figure 5 bears on this point. At the left (Fig. 5A), in a dog in which the vagi had been sectioned and the heart paced, the hemodynamic response to carotid sinus nerve stimulation is shown. The classic fall in arterial pressure is, interestingly, accompanied by a rise of mean left atrial pressure, a pattern of hemodynamic findings we have come to associate with the withdrawal of sympathetic impulses to the heart (Figure 4A after cessation of sympathetic stimulation). A more complete type of study

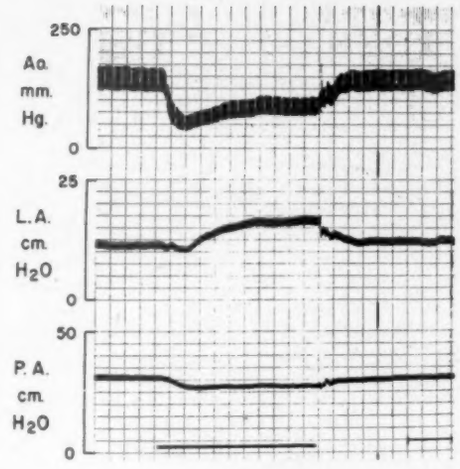

FIG. 5A. Bilateral cervical vagotomy and constant heart rate. During time indicated by bar at the bottom, the left carotid sinus nerve was stimulated. Bar at the bottom right = one minute.

is shown in Figure 5B. After vagotomy and with the heart rate held constant, pressure was raised in the carotid sinus, the latter having been converted almost completely into a cul-de-sac. With the carotid pressure high, aortic pressure, cardiac output and calculated stroke work were low in the presence of an elevated filling pressure (sympathetic withdrawal). When carotid sinus pressure was lowered, aortic pressure, cardiac output and stroke work were markedly increased while filling pressure fell (sympathetic stimulation). The observed ability of changes in carotid sinus pressure to elicit the hemodynamic changes shown in Figure 5B was, in the same dog, markedly impaired after sectioning the rami to both stellate ganglia. It was of more than passing interest that the increase in the external stroke work which was produced when carotid pressure was lowered was several times

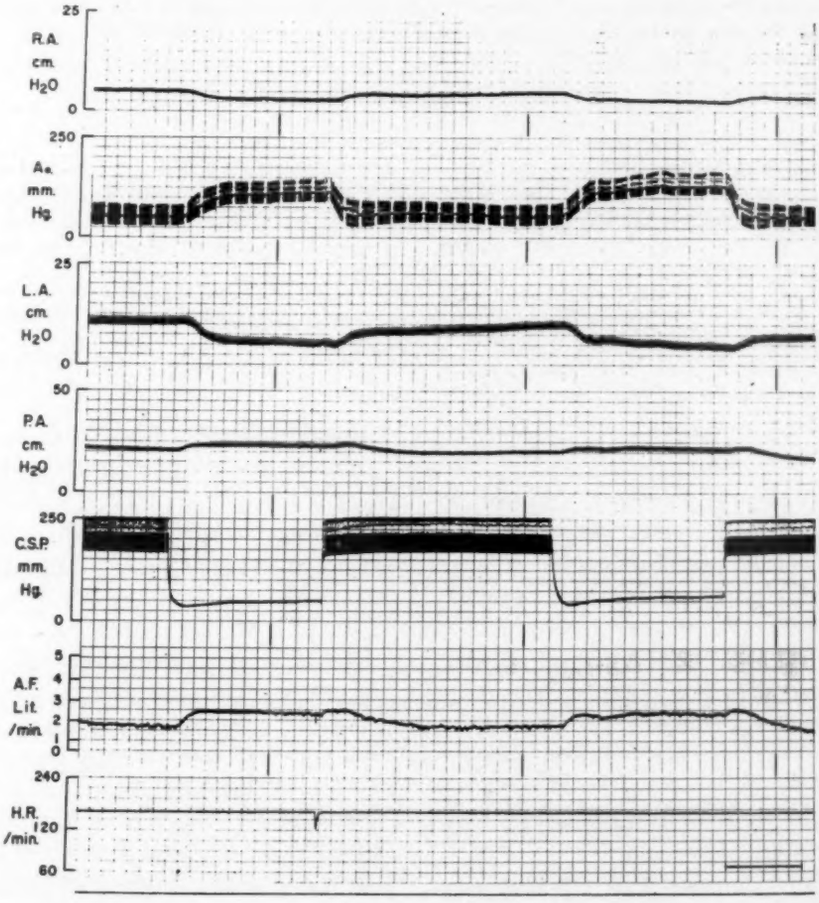

FIG. 5B. Bilateral cervical vagotomy. C.S.P. = carotid sinus pressure (produced by pump); A.F. = cardiac output minus coronary flow; H.R. = heart rate. Note the higher aortic pressures, cardiac output and calculated stroke work with lower mean left atrial pressures when carotid sinus pressure was lowered. Bar at bottom right = one minute.

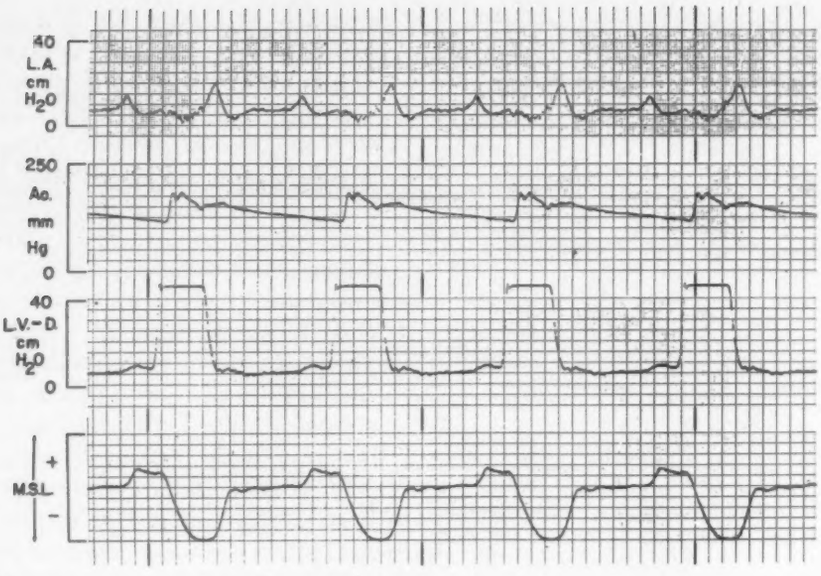

FIG. 6A. 2:1 heart block. M.S.L. = changes in myocardial segment length; + = elongation, − = shortening. L V.D. = left ventricular diastolic pressure (square topped diastolic contour is due to recording stylus coming up against its limiting stop). Note the substantial segment length increment due to the rise of ventricular end diastolic pressure with atrial systole. Chart speed = 100 mm./second.

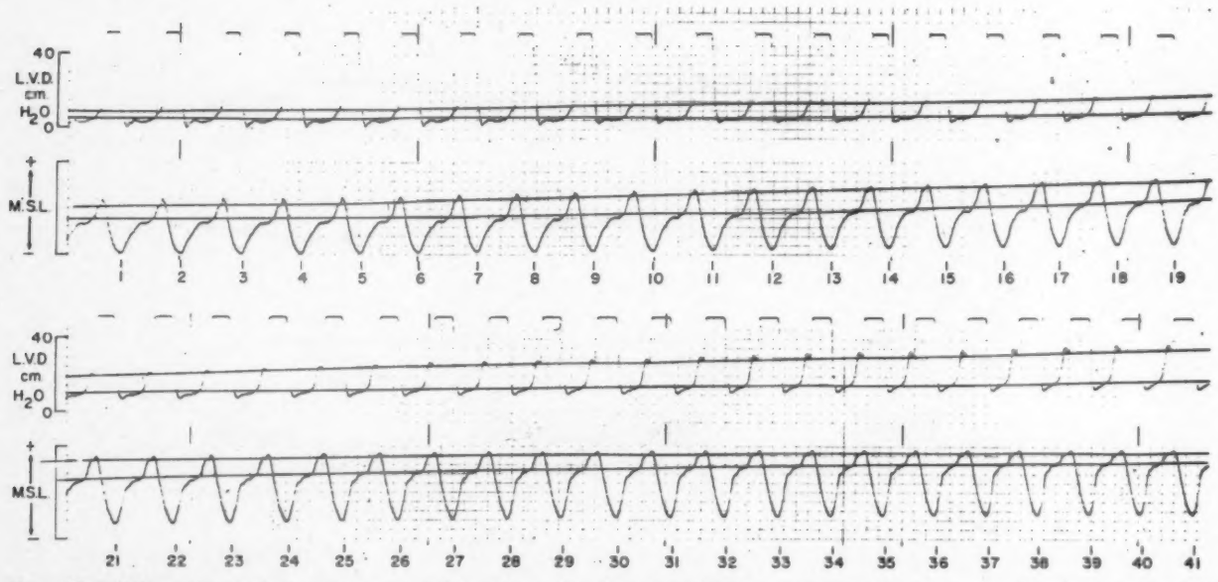

FIG. 6B. Bilateral cervical vagotomy, left stellate ganglion stimulation, constant heart rate. Continuous tracing of forty-one consecutive beats showing left ventricular diastolic pressure (L.V.D.) and changes in myocardial segment length (M.S.L.) during a rapid blood infusion. See text for explanation of transverse dark lines.

the simultaneously observed increase in total peripheral resistance.

Using the same technics and experimental approach we used when evaluating the influence of sympathetic stimulation on the position of the ventricular function curve, we next examined the influence of carotid pressure on the position of this curve. Low carotid pressures shifted the curve to the left just as with sympathetic stimulation and high carotid pressures shifted the curve to the right as when sympathetic stimulation is withheld. At intermediate carotid pressures the function curve was situated correspondingly.[7] I should also say that, just as when varying the sympathetic stimulus, if left atrial pressure changed with changes in carotid pres-

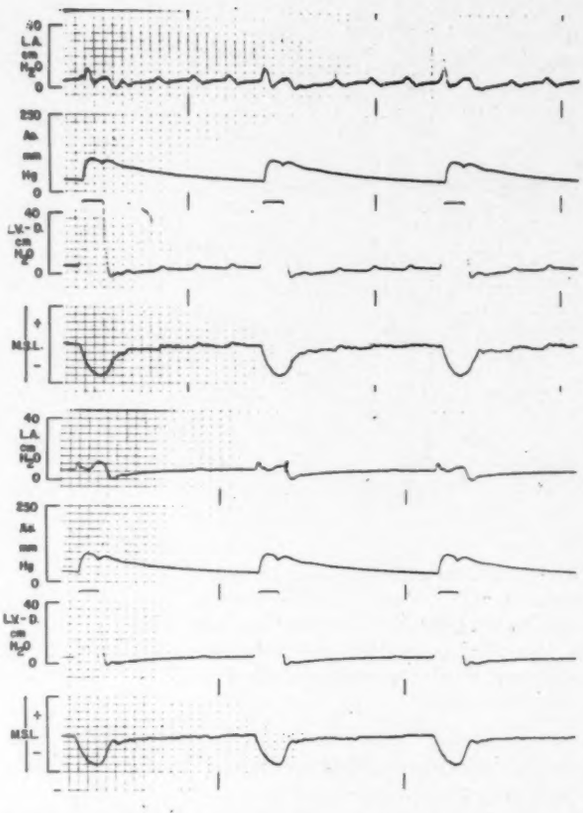

FIG. 7. Surgically induced heart block; atrium paced at constant rate throughout; bilateral cervical vagotomy. *Upper panel* taken before and *lower panel* taken during stimulation of the distal cut end of vagus nerve. Chart speed = 100 mm./second.

sure, ventricular end diastolic pressure changed similarly.

REGULATION OF ATRIAL CONTRACTION

Importance of Atrial Systole for Ventricular Filling: It seems appropriate now to return to a consideration of the effects of direct autonomic nerve stimulation on the function of the atria. Several observations (Fig. 6) have led us to believe that the vigor of atrial systole is of vastly greater importance than previously believed. In the upper tracing (Fig. 6A) one can see the rather innocuous looking increment in end-diastolic pressure produced by atrial systole (especially when it is considered that the ventricular pressure recording is greatly amplified in order to improve the resolution of diastolic pressure changes). It was of considerable interest, however, to observe the substantial increments in myocardial fiber length (M.S.L.) brought about by the atrially induced diastolic pressure changes in the ventricle.

Figure 6B gives a more complete picture of

TABLE I

Changes in Cardiac Cycle Due to Stellate Ganglion Stimulation

Analysis of Tracings Shown in Figure 9

	Control	Stellate Stimulation	% Change
Duration of atrial systole (msec.)*	120	87	−28
Duration of ventricular systole (msec.)†	270	207	−23
Duration of ventricular diastole (msec.)‡	250	313	+25
A-R interval (msec.)§	495	365	−26
Increment in left ventricular end-diastolic pressure (cm. H_2O) produced by atrial systole	2.0	6.5	+225
Duration of isometric contraction (msec.)‖	105	55	−48
Relaxation time (msec.)¶	93	75	−19

NOTE: Heart rate constant at 116/min. Total cycle time = 520 msec.

* From beginning of increase in atrial pressure until beginning of rise in ventricular pressure.

† From beginning of rise in ventricular pressure until aortic incisura.

‡ From beginning of aortic incisura to the rise in ventricular pressure.

§ A-R interval: from beginning of rise in atrial pressure to lowest point of ventricular diastolic pressure ("relaxation point").

‖ From beginning of rise in ventricular pressure until beginning of rise in aortic pressure.

¶ From aortic incisura until lowest point of ventricular diastolic pressure.

the range. It shows forty-one consecutive beats obtained during a rapid infusion of blood. In the pressure channel, lines have been drawn through ventricular diastolic pressure just before atrial systole and at the onset of ventricular systole, thus showing the end diastolic rise in ventricular pressure produced by atrial systole. Similarly, in the tracing of myocardial segment length, lines were drawn through the segment length record at a point just before atrial systole and at a point in time corresponding to the onset of ventricular systole, thus showing the elongation of fiber length attributable to atrial systole. As might have been predicted from the pressure-length curves shown in Figure 3, when ventricular diastolic pressure is low or in the normal range, atrial systole produces a large increment in fiber length; when diastolic

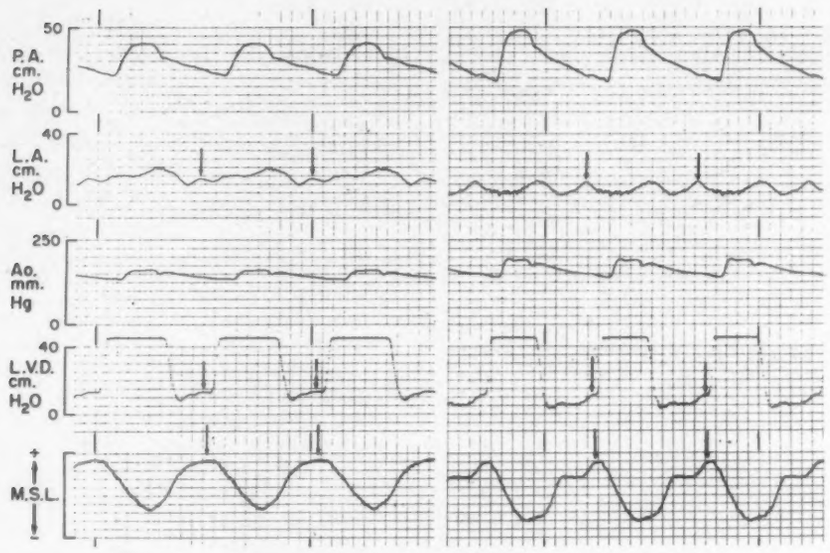

FIG. 8. Bilateral cervical vagotomy; slight vagal stimulation held as a constant background throughout; atrium paced at constant rate. Panel at left is control, panel at right taken during left stellate ganglion stimulation. Arrows indicate the augmentation in atrial systole and the increased increment in ventricular end diastolic pressure and segment length induced by the sympathetic stimulation. Chart speed = 100 mm./second. See also Table 1.

pressure is high, atrial systole will produce much less of a fiber length increment. Thus, we have been able not only to re-evaluate the general importance of atrial systole for ventricular filling and elongation of fiber length but also to describe more precisely those conditions under which it will make more or less of a contribution of this type.

Effects of Autonomic Nerve Stimulation on Atrial Contraction: With this background in view, we felt that we were more adequately prepared to undertake an evaluation of the importance of autonomic nerve stimulation on the hemodynamic activity of the atrium. Experiments of this type are shown in Figures 7 and 8. In the dog with surgically induced heart block and with the atrium being paced, the effect of *distal vagus stimulation* on atrial systole, ventricular diastolic contours and changes in segment length were observed (Fig. 7). The systole of the paced atrium was all but abolished and the reflected increment of diastolic pressure and segment length similarly affected. The inhibition of atrial systole and the reflected ventricular effects thereof produced by vagal stimulation were abolished by atropine.

Conversely, *stellate ganglion stimulation* substantially augments atrial systole and the corresponding increment in ventricular end diastolic pressure and segment length (Fig. 8). The altered events of the cardiac cycle apparent in the tracings of Figure 8 are further analyzed in Table 1.

Carotido-Atrial Reflexes: In the light of our newly acquired regard for the importance of atrial systole, the results of experiments designed to elicit carotido-atrial reflexes were of considerable interest. A tracing showing one of these, the *carotido-vago-atrial reflex*, can be seen in Figure 9A. In this dog the sympathetics were removed from the stellate ganglion through T5 and heart block was surgically induced; the vagi were undisturbed. During stimulation of the carotid sinus nerve the atrial A waves, which had been prominent in the control tracing, were all but abolished while the atrium was still being paced. The rapidity of the onset and disappearance of this phenomenon is also shown in Figure 9A. As with the effect of direct vagal stimulation on atrial contractility (Fig. 7), the carotido-vago-atrial response was blocked by atropine.

An example of the *carotido-sympatho-atrial* reflex is shown in Figure 9B, an experiment in which the vagi had been sectioned. Once again the dog with heart block was employed. After keeping carotid pressure high (pump) and noting the amplitude of the atrial A waves, carotid pressure was then lowered. The result was an increase not only in the amplitude of atrial systole but also in the reflection thereof on ventricular diastolic pressure.

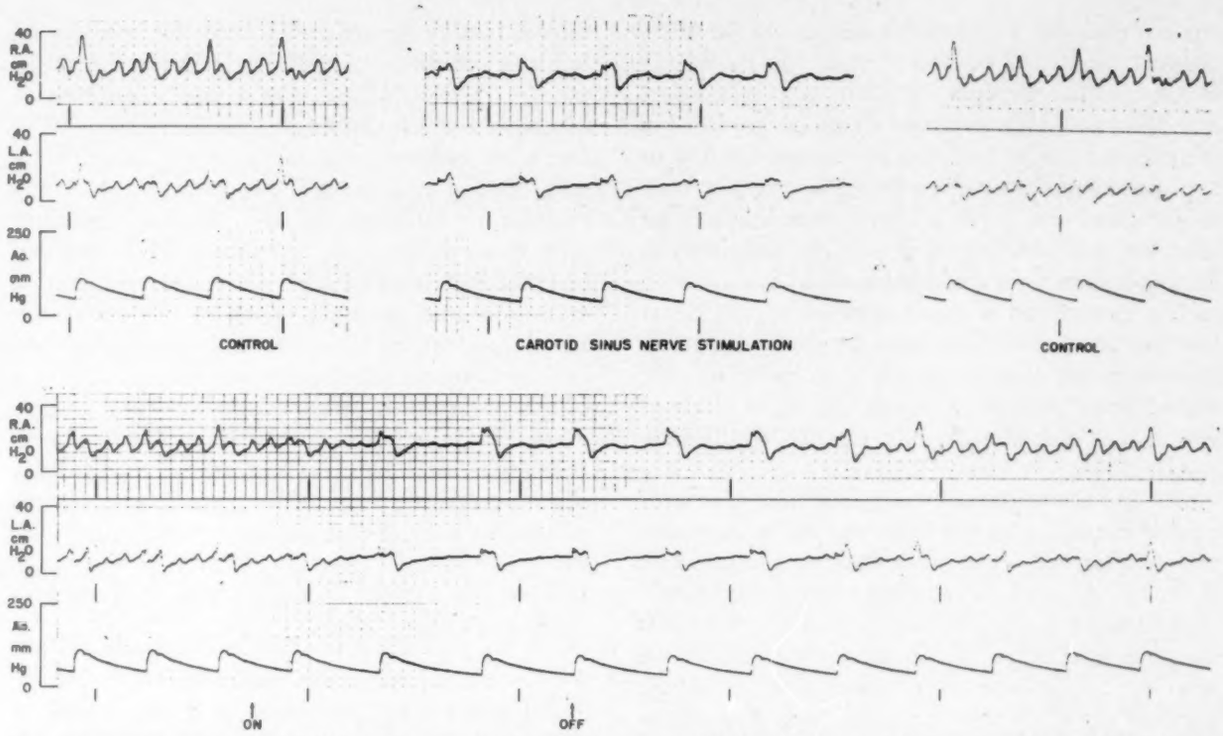

FIG. 9A. *The carotido-vago-atrial reflex.* Surgically induced heart block, atrium paced at constant rate throughout. Upper three panels show tracings obtained before, during and after stimulation of carotid sinus nerve. Lower panel shows continuous tracing during the application and rapid withdrawal of carotid sinus nerve stimulation. Sympathetics were removed from the stellate ganglia through T5 on both sides. The observed response was blocked by atropine.

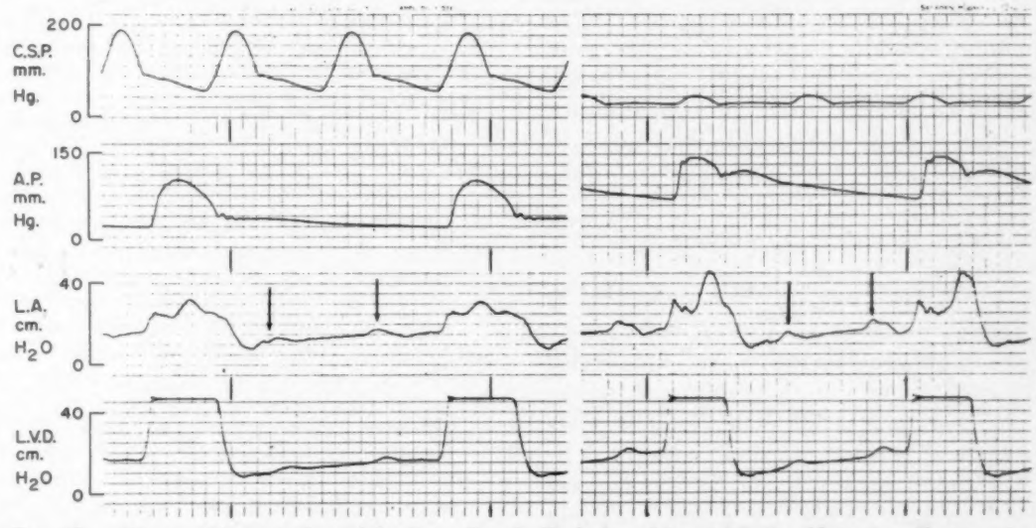

FIG. 9B. *The carotido-sympatho-atrial reflex.* Surgically induced heart block. Note the effect on the amplitude of the A waves (arrows) and ventricular diastolic pressure increments of lowering the carotid pressure. Bilateral cervical vagotomy, atrium paced at a constant rate.

PHYSIOLOGIC SIGNIFICANCE OF AUTONOMIC NERVE STIMULATION

One can conceive of the net effect of *sympathetic impulses* to the heart beating at any given rate in the following manner (Fig. 8 and Table 1). A more forceful ventricular contraction originates from any given end diastolic pressure or fiber length during sympathetic stimulation. A larger stroke volume is delivered from any given end diastolic pressure or volume. This, of course, results in more complete systolic emptying and thus places the ventricle on a lower and flatter portion of its pressure-length curve during the subsequent diastole. It is into this more receptive ventricle (that is, one which is in a lower portion of its pressure-length

curve) that an augmented atrial systole then propels blood. The more rapid development of ventricular tension, ejection and relaxation not only provides a longer diastolic period for ventricular inflow but also prevents a change in the end diastolic pressure-length curve which might otherwise occur if there were inadequate time for the dissipation of viscous and inertial factors (relaxation) during diastole.

The net effect of *vagal impulses* to the heart beating at a constant rate, at least with the intensities of vagal stimulation used in our experiments, was to diminish the vigor of atrial systole; it did not directly modify ventricular contractility.

At any given heart rate, the net effect of raising carotid pressure is to reproduce the same effects observed when withdrawing sympathetic stimulation and increasing parasympathetic stimulation; lowering carotid pressure produces the reverse effects. From these observations we are led to believe that *a dominant physiologic responsibility of the carotid sinus in circulatory regulation is to augment or diminish the contraction of the ventricle.*

The following two concise statements now appear to be appropriate for describing the manner in which the central nervous system can regulate the physical activity of the heart operating at any given rate and in the absence of abnormal conditions such as hypoxia and acidosis. We propose them as a formal means of broadening the basic Frank-Starling relationship and of integrating it with the activity of the central nervous system in relation to acutely induced changes.

(*1*) *If the effective catecholamine stimulus remains constant, the contraction of the ventricle varies directionally with its end diastolic pressure and fiber length; if the end diastolic pressure and fiber length remain constant, the contraction of the ventricle varies directionally with the effective catecholamine stimulus.*

(*2*) *The central nervous system has direct neural connections to the heart by means of which it can vary the ventricular end diastolic pressure and fiber length, or vary the effective catecholamine stimulus, or both.*

There are those among us who are keen to analyze the various mechanisms by means of which the fully competent organism so adroitly regulates the various biochemical and physical phenomena necessary for peak performance under quite widely varying conditions. So imbued are we with the elegance, and often the relative simplicity, with which nature has come to solve almost infinitely complex problems that it is easy for us to fall into the intellectual habit of unlimited confidence in her accomplishments. I must admit that I find it difficult to imagine that an organism which is deprived of the wide range of regulation made possible by catecholamine activity could even approach the circulatory competence of a similar organism with these pathways at its command. And yet, it must be remembered that the technics of evolution and biologic selection are such that nature appears to be unmindful of the adequacy of mechanisms after any substantial portion of the procreative phase of life has been passed. Thus, from the point of view of natural selection, the "evil" that catecholamines can do in later life may not live long after them insofar as this relates to survival of species. I am sure that the manner and extent to which they may do so will be the subject of subsequent presentations during this Symposium.

Acknowledgment

The data I have presented have, in every sense, resulted from the collaboration of a team of workers. My esteemed co-workers have been Drs. J. P. Gilmore, J. H. Mitchell, R. J. Linden and S. K. Brockman.

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Influence of Sympathetic Stimulation and Catecholamines on Ectopic Impulse Formation in the Ventricles of the Dog*

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THE RATE of automaticity of the cardiac centers can be increased by faradic stimulation of the sympathetic nerves or by the intravenous injection of epinephrine and norepinephrine, provided reflexes from the carotid sinus and the aortic nerves brought on by a rise in blood pressure are prevented. This increased rate of automatic impulses involves not only the centers of the sinus node but also the lower ventricular centers and may lead to a ventricular tachycardia. These ectopic tachycardias appear particularly when the vagus and sympathetic nerves are stimulated simultaneously.[1] By this procedure the higher centers are inhibited and the lower ones have a better chance to escape. These ectopic tachycardias have often been erroneously called extrasystolic tachycardias but actually represent an increased automaticity. In contradistinction to a true paroxysmal tachycardia which starts with a fixed coupling to a normal beat of the basic rhythm, this form of ectopic ventricular tachycardia is characterized by a gradual replacement of the existing sinus rhythm by the ectopic rhythm.

While epinephrine and related substances increase the automaticity of the cardiac centers, the extrasystolic impulse formation in the form of single or multiple extrasystoles or extrasystolic tachycardias may be abolished or be provoked and accelerated by the same substances.

INCREASE IN NUMBER OF EXTRASYSTOLES

It has been known for about fifty years that when the heart is sensitized with barium or calcium chloride, or in the course of anesthesia with chloroform, sympathetic stimulation or epinephrine provokes extrasystoles, ventricular tachycardias or even ventricular fibrillation. This is due primarily to the direct effect of epinephrine on the heart muscle. Excitability and vulnerability are increased[2] and extrasystolic impulses are formed. Indirect effects caused by the rise of the blood pressure also contribute.

Barium Chloride: If a 5 per cent solution of barium chloride is applied topically to the surface of the right ventricle of the exposed heart of a dog a ventricular tachycardia appears, which is replaced by a sinus rhythm after a few minutes. When, at this time, the right or left sympathetic nerves of the animal are stimulated the ectopic tachycardia reappears with an increased rate.[3]

Aconitine: Atrial flutter is readily created by focal application of aconitine on any part of the dog's atria. It has been demonstrated that this type of flutter is caused by a rapid impulse formation at the point of application.[4] Faradic stimulation of the right or left sympathetic nerves causes an increase of the rate of flutter. Thus in Figure 1 aconitine had been applied on the tip of the appendix of the right atrium. Flutter with a rate of 375 per minute resulted. Stimulation of the right cardiac sympathetic nerves which were isolated from the sympathetic chain resulted in an increase of the rate of flutter to 428 per minute.[5]

Sodium Chloride: Ectopic ventricular extrasystoles and tachycardia are readily produced by focal application of concentrated solutions of

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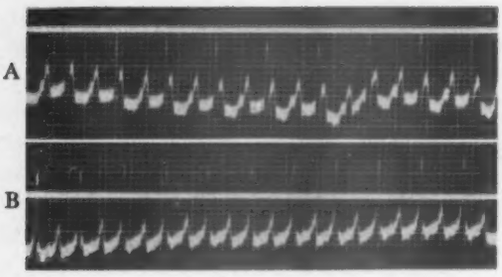

FIG. 1. A, atrial flutter provoked by focal application of aconitine to the right atrium. B, faradic stimulation of the right sympathetic nerves increased the atrial rate from 375 to 428 per minute. All tracings are registered in lead II.

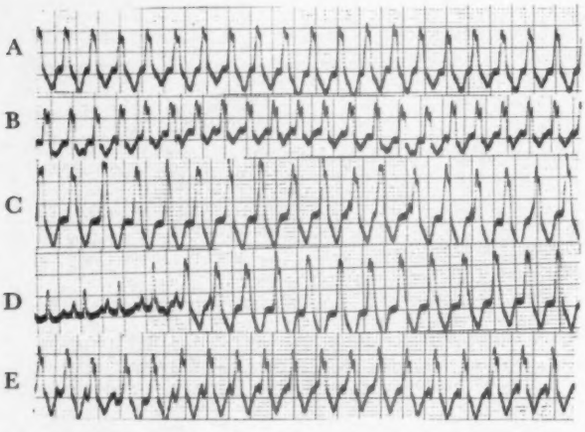

FIG. 2. A, ventricular tachycardia appeared after focal application of a 20 per cent solution of sodium chloride to the right ventricle; rate is 240 per minute. B, the intravenous injection of 0.02 cc. per kg. of epinephrine standard solution changed the form of the ventricular complexes and increased the rate only to 250 per minute. C, tracing obtained about three minutes later, showing the same form of ventricular complexes as before the injection; the rate is 214 per minute. D, a ventricular tachycardia reappeared when the same salt solution was applied to the same area about fifteen minutes later; the rate is 214 per minute. E, the intravenous injection of 0.01 cc. per kg. of epinephrine increased the rate to 230 per minute.

sodium chloride.[3] The extrasystoles and the ectopic tachycardias show constant coupling. In the experiment illustrated in Figure 2 such a regular tachycardia was present (Fig. 2A). The injection of 0.02 cc. per kg. of a standard solution of commercial epinephrine into the jugular vein caused a slight change of the form of the QRS-T complexes but the rate rose only from 240 to 250 beats per minute (Figs. 2B and 2C). Fifteen minutes later the experiment was repeated except that 0.01 cc. per kg. of epinephrine was injected. The result was the same (Figs. 2D and 2E).

Sodium Oxalate or Citrate: A classic method to provoke repetitiveness in nerve and skeletal

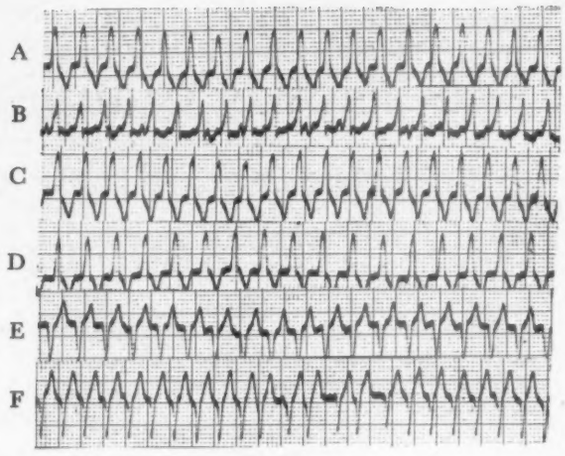

FIG. 3. A, a regular ventricular tachycardia had appeared after focal application of a 3.8 per cent solution of sodium oxalate on the right ventricle; the rate is 250 beats per minute. B, the intravenous injection of 0.01 cc./kg. of epinephrine changed again the form of the ventricular complexes and the rate increased to 280 per minute. C, D, in the next few minutes it slowed down to 250 and 230 per minute. E, twenty minutes later the same solution was applied on the left ventricle; a ventricular tachycardia appeared with a rate of 280 per minute. F, it increased to 300 per minute with some irregularities when 0.02 cc./kg. of epinephrine was injected.

muscle is decalcification by application of sodium oxalate or sodium citrate. Focal application of these compounds to the ventricles of the dog's heart provokes extrasystoles with fixed coupling and ventricular tachycardias.[6] Figure 3A shows a ventricular tachycardia caused by the injection of 0.05 cc. of a 3.8 per cent solution of sodium oxalate in the conus area of the right ventricle of a dog. An intravenous injection of 0.01 cc. per kg. of the epinephrine solution causes only a moderate increase of rate from 250 to 280 per minute (Fig. 3B). The form of the QRS complexes is again altered at the height of the action of epinephrine. The original rate and pattern of the electrocardiogram reappeared within the next four minutes (Figs. 3C and 3D). The same solution of sodium oxalate was applied to the left ventricle and elicited a tachycardia with a rate of 280 per minute. The injection of epinephrine increased the rate to 300 per minute (Figs. 3E and 3F).

It is of interest and of practical importance that ventricular fibrillation did not occur in any of these experiments.

These experiments show that the rate of ectopic tachycardias caused by application or administration of barium chloride, aconitine, sodium oxalate and sodium chloride can be in-

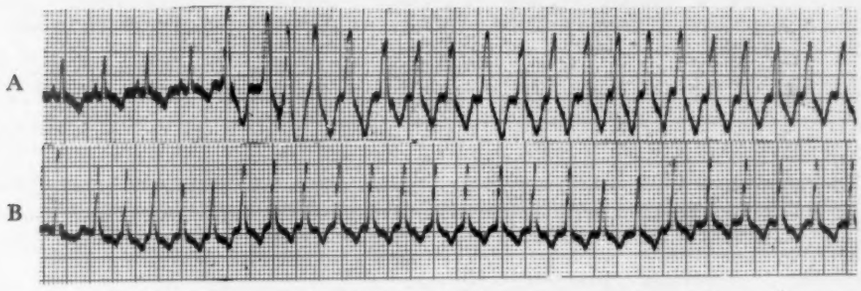

FIG. 4. A, beginning of a ventricular tachycardia which appeared after striking an area of the conus of the right ventricle with a blunt instrument. Nicotine had been applied one minute previously. B, the same type of tachycardia obtained in the same manner in another experiment after focal application of epinephrine.

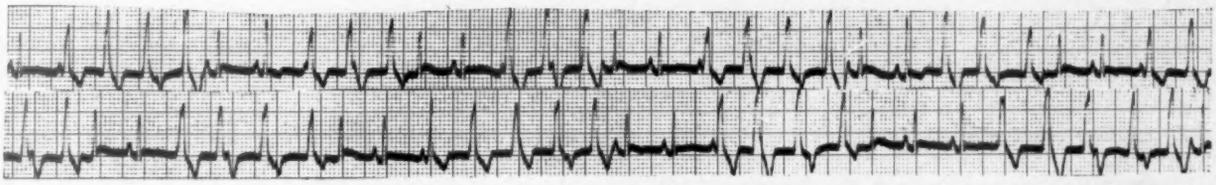

FIG. 5. The two strips show a parasystolic rhythm which appeared spontaneously after focal application of epinephrine to the right ventricle.

creased by administration of epinephrine or sympathetic stimulation but the increase is often moderate.

We believe that these extrasystoles are caused by oscillatory after-potentials following repolarization of the cell membrane. Of interest in connection with our results is the finding of Bozler[7] that, in the injured and depressed turtle's heart, epinephrine increases the magnitude of the after-potentials but does not influence their rate.

AFTER-DISCHARGE

Application of Nicotine: The phenomenon of after-discharge, that is, the firing of a series of impulses following one stimulus, is often seen after application of epinephrine. We were led to the study of this phenomenon by the result of investigations on the action of nicotine applied directly to the cardiac surface. Two effects are seen with this method of drug administration. One is the local one, which is drug-specific and leads to different arrhythmias characteristic for the substance applied; the other effect is systemic and is caused by the rapid absorption of nicotine from the cardiac surface. This effect consists of the well known phenomena of increased cardiac contractility, diminution of cardiac size, increase of arterial blood pressure, bleeding of arteries, etc. Due to the local effect of nicotine, ectopic tachycardias appear often and last several minutes. After spontaneous tachycardias disappear or just before their appearance they can readily be provoked by one stroke with a blunt instrument to the area on which the nicotine was applied (Fig. 4A) but not by striking any other area. These tachycardias are very regular; before they disappear a gradual slowing of rate is observed. After they disappear vagus stimulation permits the ectopic tachycardia to be seen again.

Mechanical Stimulation: Since nicotine leads to the release of catecholamines (epinephrine and norepinephrine) in the heart which may accumulate in the heart muscle,[8] we studied the effect of mechanical stimulation of an area of heart muscle pretreated by focal application of 0.05 cc. of the standard solution of epinephrine injected subepicardially. The effect was identical to that observed after administration of nicotine (Fig. 4B). Long chains of ectopic tachycardia appeared and in one experiment the tachycardia lasted for 632 beats. The first few beats were fast and then the rate remained unchanged until the tachycardia slowed down before its disappearance. Mechanical stimulation of other areas of the same and the other ventricle did not show this effect.

In three experiments a true parasystolic rhythm appeared spontaneously after the focal injection of epinephrine (Fig. 5). The ectopic center interfered with the sinus rhythm and the interectopic intervals during the sinus rhythm were multiples of the minimal intervals between two successive ectopic beats.

These results are of interest in connection with a clinical experience. One of the simpler methods of resuscitation during standstill of the heart is the application of blows to the precordium. The normal heart responds to every blow with one extrasystole. In a clinical study[9] of this response in patients with Morgagni-Stokes-Adams attacks or cardiac standstill occurring in some patients with myocardial infarction the observation could be made that with succession of many attacks or after prolonged bradycardia and standstill the heart responded to one blow with a succession of rapid beats just as in these experiments after application of epinephrine. Since one may assume that under the conditions mentioned large amounts of epinephrine are secreted, it is possible that their accumulation in the myocardium is one of the factors responsible for the multiple response.

Decrease in the Number of Extrasystoles

If extrasystoles and extrasystolic tachycardias are provoked in the dog's heart by intravenous administration of minute doses of aconitine these arrhythmias will always be temporarily abolished by stimulation of the sympathetic nerves.[10] Experiments performed many years ago showed that epinephrine, given intravenously has the same effect.[11] In rare instances the disappearance of extrasystoles will be preceded by an increase of their number and a bigeminal rhythm may be changed into a ventricular tachycardia for a few beats. After two to three minutes the extrasystoles always recur. In all experiments the sinus rhythm is accelerated by the sympathetic stimulation in the normal manner and the tracings show clearly that the extrasystoles are actually suppressed and do not vanish because of the increase of rate. These findings were later confirmed by others.[12,13]

When the sympathetic nerves are stimulated the disappearance of extrasystoles caused by intravenous administration of aconitine is in contrast to the increase of rate of flutter caused by focal administration of aconitine mentioned before. This observation confirms the fact that impulse formation in flutter caused by administration of aconitine cannot be compared with that in extrasystoles or paroxysmal tachycardias. The response of these arrhythmias to vagus stimulation and the reaction to many drugs is also different.

Following the intravenous injection of thiobarbiturates in the dog ventricular bigeminal rhythm usually appears. It is immediately abolished by administration of epinephrine or norepinephrine.[14,15]

Comments

The faculty of different catecholamines to provoke ectopic rhythms has been widely studied[16,17] in different animals and in human patients. Little is known about the effect of these substances on existing ectopic cardiac rhythms. This question is of importance since in myocardial infarction ectopic rhythms often appear and development of shock may make the use of catecholamines necessary. In a review of the cardiovascular effects of some commonly used pressor amines, Aviado[16] states that mephentermine "is the only pressor agent which stimulates the sino-auricular node, yet prevents or stops experimental arrhythmias." Our experiments show that commercial epinephrine may have the same action. It is evident that ectopic rhythms provoked by different means respond differently and therefore many generalizations are not permissible.

In man the disappearance of extrasystoles and paroxysmal tachycardias can also be observed after administration of any of the known pressor amines but there is no doubt that the employment of milder agents such as mephentermine, Vasoxyl® or isoproterenol is less dangerous.[13,18,19] All catecholamines may abruptly end a bout of paroxysmal tachycardia even of the ventricular type but their administration is recommended only in the presence of shock when emergency measures are indicated. Otherwise their use is not justified. During the transitional period, at the height of their action where the catecholamines abolish an existing tachycardia, other ectopic beats appear which may assume dangerous proportions and lead to fibrillation. In this respect pressor amines are similar to other substances applied intravenously in ectopic tachycardia, such as quinidine or procaine amide and potassium, calcium and magnesium salts, which also suppress one focus but create new ones.

The experience that existing ventricular tachycardias were not converted into ventricular fibrillation, that actually they are little influenced or even abolished by epinephrine given intravenously in large doses, encourages the clinical use of pressor amines in patients with arrhythmias in shock.

Summary

Ventricular tachycardia provoked by focal

application of hypertonic solutions of sodium chloride on the exposed heart of the dog is little influenced by the intravenous injection of 0.01 to 0.02 cc. per kg. of the commercial solution of epinephrine. Only a moderate acceleration of the rate is seen when epinephrine is injected in the same dosage after a ventricular tachycardia was obtained by focal application of sodium oxalate.

In no experiment did epinephrine elicit ventricular fibrillation.

These results and the experience that extrasystoles and tachycardias caused by administration of aconitine are abolished by administration of epinephrine or sympathetic stimulation encourage the use of the less stormily acting pressor amines in patients with ectopic arrhythmias and shock.

Under the influence of nicotine or epinephrine applied focally, one mechanical impulse causes a long after-discharge in the form of chains of ectopic beats. The clinical implications of this finding are discussed.

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Effect of Epinephrine and Norepinephrine on the Electrocardiogram of 100 Normal Subjects*

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P. de Paula e Silva, M.D.§ *and* W. Raab, M.D., F.A.C.C., with the technical assistance of Y. K. Starcheska

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Several years ago a large number of normal pregnant and non-pregnant women were subjected to standardized intravenous infusions of epinephrine and norepinephrine to study the causal mechanism of toxicosis of pregnancy and to develop a possible screening test for pretoxemia.[1] Electrocardiograms were registered before and during the infusions, but a detailed analysis of electrocardiographic findings was reserved for a later time. The purpose of the present paper is to carry out such an analysis, correlating the electrocardiographic changes with those of the heart rate and blood pressure. To obtain further insight into the mechanism of these changes, the electrocardiograms taken during infusion of these substances before and after administration of atropine in a series of normal young men[2] were also analyzed. The results of these two series are interpreted in the light of observations in experimental animals.[3–6]

Material and Methods

The first group of observations included sixty apparently healthy young women between ages of sixteen and thirty-nine years. Of these, thirty-three were pregnant. In each, electrocardiograms and blood pressures were first recorded in the recumbent position during infusion of isotonic dextrose solution, after the blood pressure values had stabilized. Without the knowledge of the subject, the infusion was then changed to a similar solution containing l-norepinephrine, delivered at the rate of 0.2 μg. per kg. body weight per minute, and electrocardiograms and blood pressures were again recorded three minutes after the start of this infusion. Five minutes after beginning the infusion the solution was replaced by isotonic dextrose solution, and the blood pressure measured in one-minute intervals until it had returned to preinfusion levels and become stable. The procedure was then repeated, using epinephrine at a rate of 0.2 μg. per kg. per minute, and subsequently 0.3 μg. per kg. per minute norepinephrine and epinephrine, respectively. The electrocardiograms were registered on a four-channel Sanborn Poly-Viso instrument, in two sets of synchronous tracings consisting of leads I, II, III and the heart sounds, and four precordial leads, respectively. Details of the dosage and infusion technic can be found in an earlier publication.[1]

The second group of observations pertained to forty normal young men (twenty of them active athletes) in whom infusions of 0.1 μg. per kg. per minute norepinephrine and epinephrine were carried out in the same manner as in the young women. After these infusions, 0.025 mg. per kg. of atropine sulfate was injected intravenously and after seven minutes the infusion of epinephrine was repeated and the blood pressure measured at intervals until it returned to preinfusion levels; this took place usually within ten to fifteen minutes. At this time another electrocardiogram was registered in order to obtain a second baseline for the following infusion, and the infusion

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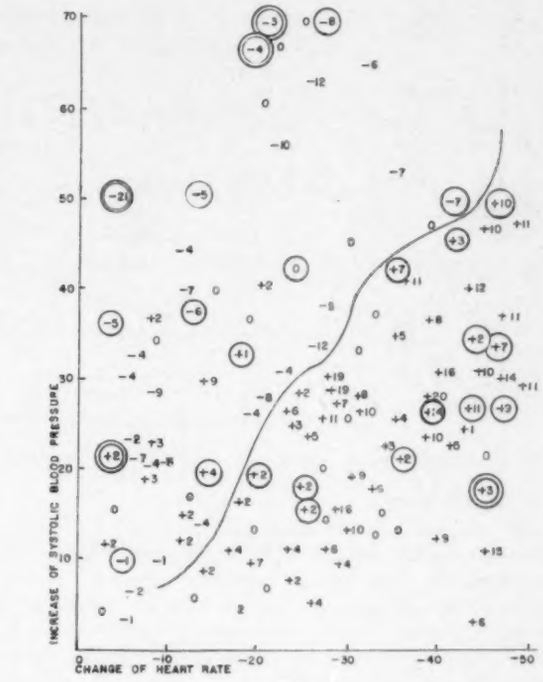
of norepinephrine was repeated. Norepinephrine was given last since in some of the subjects (not included in the forty subjected to analysis) the infusion of this substance had to be interrupted because of appearance of severe headache. In this series, leads II and V_4 of the electrocardiogram were registered together with the heart sounds and the carotid pulse.

Results

HEART RATE AND RHYTHM

Heart Rate: Infusion of norepinephrine caused a decrease in the heart rate in all patients. In the women the average decrease was 19 with the 0.2 μg. dose and 26 with the 0.3 μg. dose. With the same dose, it tended to be greater in persons having a high heart rate at rest. In the young men and with the 0.1 μg. dose it was 12 in the athletes and 10 in the non-athletes. In Figure 1, where this change in heart rate is plotted against the increase in systolic blood pressure, only a slight relation between these two variables is apparent. This can be explained by the fact that, although the decrease of heart rate is caused by reflex vagal stimulation from the pressoreceptors as a result of the rise in blood pressure, this stimulation in itself leads to a decrease of pressure. After administration of atropine, infusion of norepinephrine caused an increase in heart rate in all but three of the forty men, and the decrease in these three was only five beats; the increase in blood pressure, on the contrary, was five times greater after administration of atropine.

After infusion of epinephrine, the heart rate rose in the great majority of the young women; the average change of rate was an increase of 8 after the 0.2 μg. dose and 12 after the 0.3 μg. dose. Figure 1 shows that a decrease is likely to be accompanied by a marked increase in systolic blood pressure, while a marked increase is usually accompanied by a slight increase in pressure. However, at equal systolic pressures the heart rate is about 25 beats faster during infusions of epinephrine than during those of the same amount of norepinephrine. In the group of young men infusion of 0.1 μg. of epinephrine caused an increase of heart rate in all but one of the forty persons; the average increase was 17 in the athletes and 15 in the non-athletes. The higher value for this smaller dose than for the higher doses given in women is probably due to the fact that with this dose the average increase in systolic pressure almost exactly equaled the decrease in diastolic pres-



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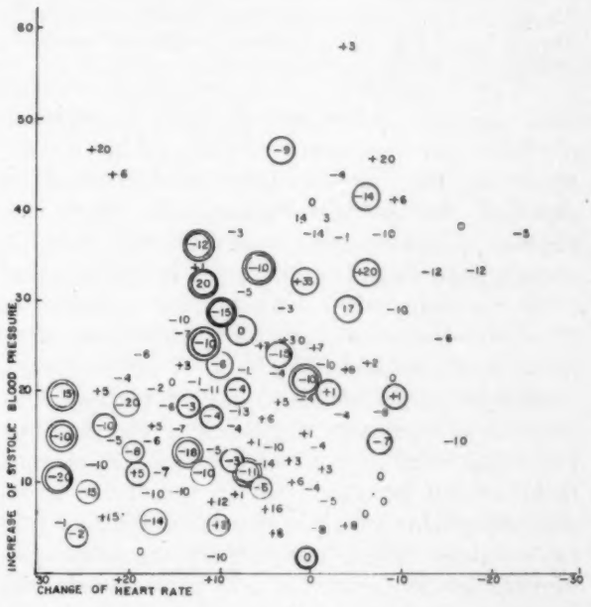

B

FIG. 1. A, changes in amplitude of the T wave (in 0.1 mm. or 0.01 mv.) in lead II under the influence of norepinephrine, 0.2 and 0.3 μg. per kg. per minute in sixty normal women, plotted against the change in systolic blood pressure and heart rate. To the left of the curved line elevation exceeding 0.4 mm. does not occur while to the right of it there is no decrease in voltage. Single circles indicate diphasic or inverted T waves in lead V_2 only, while double circles indicate the same changes of T in another additional lead (II, V_4 or V_6). B, similar graph for epinephrine, 0.2 and 0.3 μg. per kg. per minute.

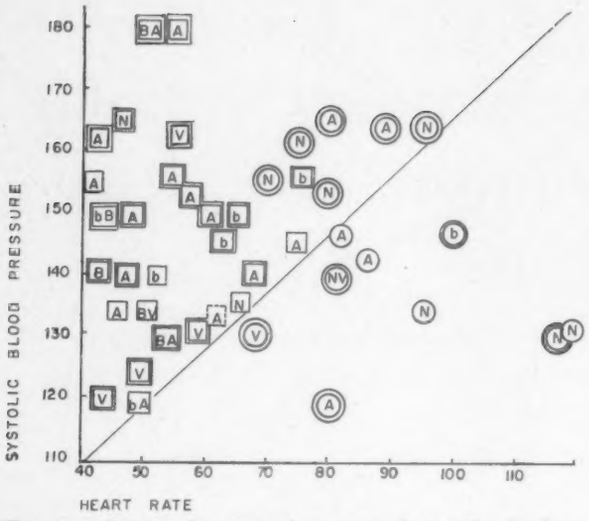

FIG. 2. Conduction disturbances and ectopic rhythms registered during infusions of epinephrine and norepinephrine in 100 normal persons, correlated to the systolic blood pressure and heart rate at the time of their appearance. A = atrial ectopic rhythms. B = atrioventricular block. b = sinoatrial block. N = A-V nodal ectopic rhythms. V = ventricular ectopic rhythms. Dotted square = norepinephrine, 0.1 μg. per kg. per minute. Single square = norepinephrine, 0.3 μg. per kg. per minute. Single circle = epinephrine, 0.2 μg. per kg. per minute. Double circle = epinephrine, 0.3 μg. per kg. per minute.

sure, so that reflex effects from the pressoreceptors are practically absent. This is supported by the fact that after administration of atropine the average increase in heart rate caused by epinephrine was only very slightly greater than before atropine (18 in athletes and 17 in non-athletes). This increase was greater than in the case of norepinephrine after infusion of atropine (10 and 4, respectively).

Respiratory Arrhythmia: The degree of respiratory arrhythmia (fluctuations of the heart rate, expressed as a percentage of the average rate) always increased under the influence of norepinephrine in all doses. Epinephrine had no constant effect, but usually increased this percentage whenever it led to a substantial decrease of heart rate. After administration of atropine arrhythmia practically disappeared in all subjects. The increased respiratory arrhythmia during infusion of norepinephrine could be related to the observation that respiratory oscillations of systolic blood pressure were more apparent during auscultatory blood pressure measurements at that time. This, in turn, could be explained by assuming that increased peripheral resistance causes respiratory changes in cardiac filling and output to lead to greater changes of blood pressure.

Ectopic Arrhythmias: The types of arrhythmia found during infusions of epinephrine and norepinephrine are summarized in Figure 2. It can be seen that during infusions of norepinephrine ectopic rhythms appeared only at high blood pressure levels and at low heart rates (only to the left of a diagonal line in Figure 2 corresponding to a value of 70 for systolic blood pressure less heart rate). It is probable that the greater stretching of cardiac muscle accompanying elevation of blood pressure increases cardiac automaticity and decreases the preautomatic pause necessary for the appearance of escape rhythms; this effect of stretching has been repeatedly demonstrated experimentally.[7] On the other hand, arrhythmias due to infusion of epinephrine appear at all heart rates, but also tend to favor the higher blood pressure ranges. In other words, the ectopic rhythms caused by administration of norepinephrine are largely passive while those caused by infusion of epinephrine tend to be active; this is in keeping with the higher incidence of arrhythmias after infusion of epinephrine as compared to that after norepinephrine was given to atropinized cats.[8]

P WAVE

The amplitude of the P wave usually decreased under the influence of norepinephrine and increased under that of epinephrine, so long as sinus rhythm was present. Epinephrine also caused the P-R segment in leads with positive P waves to show increased negative displacement and a downward course. Part of these changes were due to superposition of the P wave and the P-R interval on the descending branch of an elevated U wave, but they were also present when a decrease of heart rate allowed adequate separation between these waves.

P-R INTERVAL

The P-R interval showed a slight decrease whenever the heart rate increased and a slight increase whenever it decreased, but it became prolonged beyond the upper limits of normal for the heart rate[5] only under the influence of norepinephrine and in only three persons; in these the rise of systolic blood pressure exceeded 40 mm. Hg. The P-R interval was also prolonged in all subjects designated as showing A-V block in Figure 2, since this block always appeared as Wenckebach periods; in these subjects the block also appeared only at high

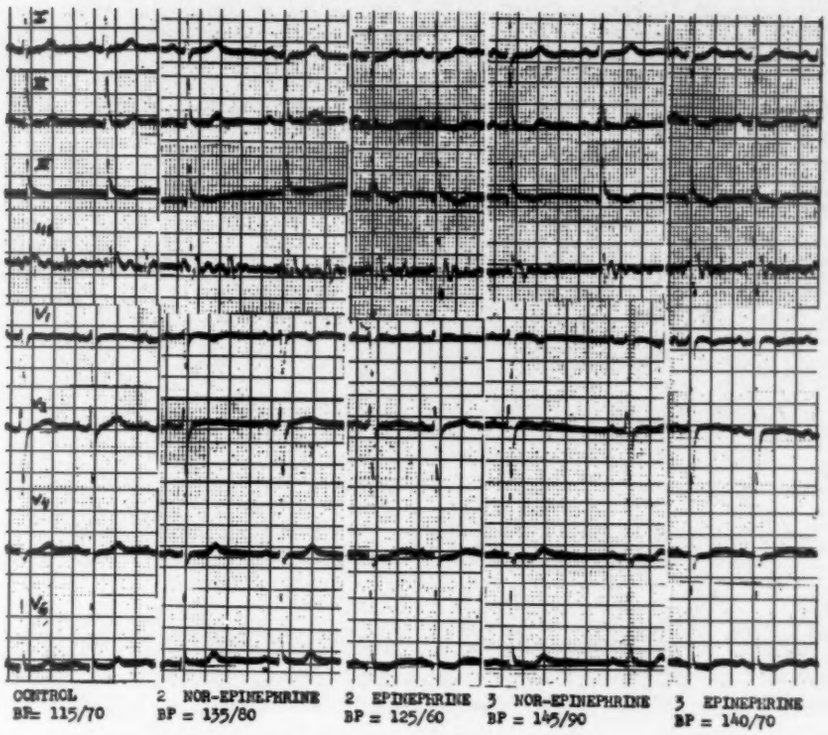

FIG. 3. Electrocardiogram and heart sounds (HS) of a twenty-three year old healthy non-pregnant woman during infusion of 0.2 and 0.3 μg. per kg. per minute of norepinephrine and epinephrine (BP = blood pressure). This illustrates pronounced T wave changes accompanying marked hypertensive effect of norepinephrine, as well as typical changes of the T wave, S-T segment and U wave caused by infusion of epinephrine.

blood pressure values or low heart rates. This dependence indicates that the conduction disturbance was of vagal origin.

QRS COMPLEX

The QRS complex usually showed increased amplitude and slight axis deviation to the right in the frontal plane under the influence of both norepinephrine and epinephrine. These changes are probably caused at least in part by a more inspiratory position of the diaphragm.[5] The QRS interval could be measured accurately only in the tracings of the young men, which were taken at double paper speed. This interval showed no changes beyond the usual slight inverse relation to the heart rate.[5]

T WAVES

The most constant and clinically important changes of the ventricular complex concern the T wave, S-T segment and U wave, and these are quite different for epinephrine and norepinephrine.

Effects of Norepinephrine: In the young women, administration of 0.2 μg. norepinephrine caused elevation of the T wave in lead II in thirty-eight, no change in ten and decreased voltage in twelve, while infusion of 0.3 μg. norepinephrine caused increase in voltage in twenty-nine, no change in eleven and decrease in nineteen. In most subjects the T wave was lower during the infusion of the 0.3 μg. dose than during that of the 0.2 μg. dose. In Figure 1, where the changes in the voltage of the T wave are plotted against the changes in blood pressure and heart rate, it can be seen that the greatest changes of the T wave in a positive direction tended to appear when slowing of the heart was greatest, and that at the same degree of slowing a decrease was likely to appear when the increment of blood pressure was high. This relation to the blood pressure also explains the paradoxical behavior of the T wave at higher doses. The voltage of the T wave in leads I, III, V_4 and V_6 showed approximately the same behavior as that in lead II.

Inversion or diphasic form of the T wave in lead II was not observed, but diphasic form in lead V_4 was observed in four subjects and in V_6 in two subjects, both only after the higher dose (Fig. 3). These subjects (double circles

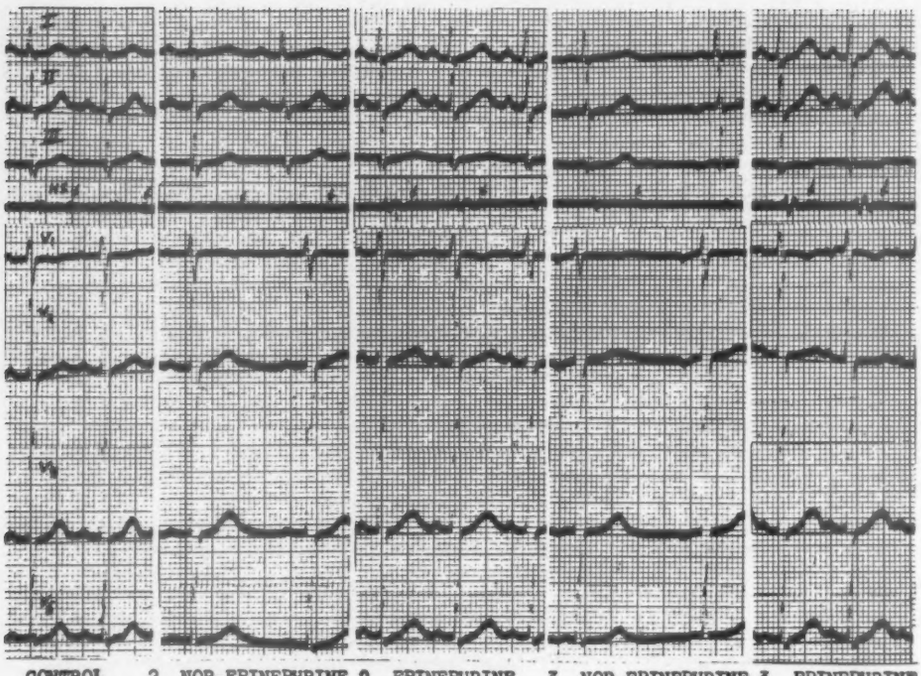

FIG. 4. Electrocardiograms and heart sounds (HS) of a normal eighteen year old woman in the thirty-first week of a normal pregnancy, during infusion of 0.2 and 0.3 μg. per kg. per minute of norepinephrine and epinephrine. This illustrates marked elevation of the T wave due to superposition on, and almost complete fusion with, greatly elevated U waves. The second heart sound (marked by arrows) indicates the boundary between the T and U waves; this boundary can also be seen in the form of a notch or kink in leads II and V_2 to V_6. During infusion of the higher dose of norepinephrine an ectopic lower atrial rhythm appears.

in Figure 1A) showed a decrease or only an insignificant increase in the voltage of the T wave in lead II, and all except one corresponded to large increases in blood pressure. In lead V_2 the T wave was diphasic or inverted at rest in five persons of the sixty; this finding is not uncommon in pregnancy,[5] and all these persons were pregnant. Inversion or diphasic form of the T wave in lead V_2 appeared after the 0.2 μg. dose in seven persons and after the 0.3 μg. dose in eighteen persons. According to Figure 1A, this behavior was accompanied by increase of voltage of the T wave in lead II as often as by a decrease, and appeared at all ranges of heart rate or blood pressure. Notching of the T wave in lead V_2 was seen in seven subjects after the 0.2 μg. dose and in eleven after the 0.3 μg. dose; it showed no definite relation to voltage changes in lead II, heart rate or blood pressure. Since, in most of the subjects inversion, diphasic form or notching of the T wave in lead V_2 only was accompanied by decrease of the R/S ratio in the same lead, it is probable that this change of configuration was caused by a more inspiratory position of the diaphragm, which resulted in lead V_2 facing a higher region of the heart where inverted or diphasic T waves are a normal finding.

After the 0.1 μg. dose of norepinephrine in young men, the T wave in lead II became higher in twelve, showed no change in seventeen and became lower in eleven; the average change was +0.04 mm. The behavior of the T wave in lead V_4 was similar. Inversion of the T wave did not occur in any of the registered leads. After atropine had been given, it caused elevation of the T wave in sixteen, no change in four and decreased voltage in twenty; the average change was −0.32 mm. in athletes and −0.03 mm. in non-athletes. To determine how much of these changes was caused by the change in heart rate and how much by the specific effect of norepinephrine, the change in T wave voltage for every ten beats change of heart rate was determined. According to the work of Sjöstrand,[9] the voltage of the T wave in a given person shows a linear inverse relation to the heart rate. In lead II the average de-

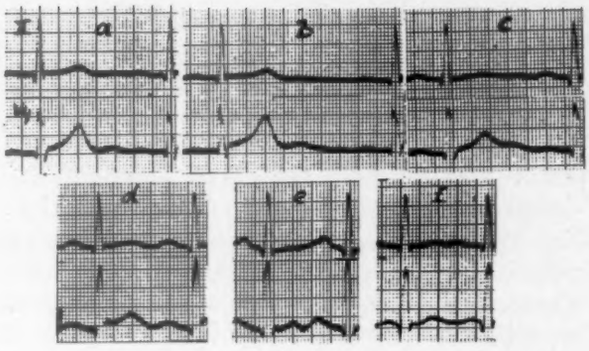

FIG. 5. Electrocardiogram of a normal twenty-three year old man. Double paper speed. (*a*) Control. (*b*) During infusion of 0.1 μg. per kg. per minute of norepinephrine. (*c*) During infusion of 0.1 μg. per kg. per minute of epinephrine. (*d*) After atropine. (*e*) During infusion of same dose of epinephrine after atropine. (*f*) During infusion of same dose of norepinephrine after atropine.

crease in height of the T wave due to tachycardia as a result of pure vagal inhibition due to administration of atropine was 0.40 mm. for every change of ten beats. However, the increase in voltage of the T wave accompanying decrease of heart rate due to infusion of norepinephrine before administration of atropine was only 0.04 mm. per ten beats; accordingly, the specific effect of norepinephrine, apart from the indirect effect of the slowing of the heart caused by it, must have been to decrease the voltage of the T wave.

Effects of Epinephrine: In the group of normal women, infusion of epinephrine caused elevation of the T waves in lead II in twenty-five, no change in eight and decreased voltage in eighty-seven tests. When the changes in the T wave are plotted against those of blood pressure and heart rate (Fig. 1A), no definite correlation can be seen. However, inspection of the tracings (Fig. 4) shows that in all subjects whose T waves appeared elevated after epinephrine was given these waves were not pure T waves but combination waves resulting from a nearly complete fusion of the T wave and a greatly elevated U wave or "after-potential." This could be clearly demonstrated by the fact that the second heart sound appeared considerably earlier than the apex of this wave, at the time of a notch or kink that could be distinguished in at least some of the leads. In some cases fusion of the T and U waves was incomplete during infusion of the smaller dose but complete during that of the larger dose. It is probable that the decrease in voltage or inversion of T waves in the subjects who showed these changes would have been even greater if the T waves were not superimposed on elevated U waves. Inversion or diphasic configuration of the T wave in lead II occurred in six subjects after the lower and in eight subjects after the higher dose; in four subjects this was accompanied by inversion of the T wave in lead V_6 (Fig. 3) while in one subject inversion occurred only in lead V_6. In these subjects the T wave was usually low at rest and the increase in heart rate was considerable. Inversion or diphasic form of the T wave in lead V_2 only was present in twenty-two subjects after both the lower and the higher dose.

In the group of young men, infusion of 0.1 μg. per kg. per minute of epinephrine caused a decrease in voltage of the T wave in lead II in all forty subjects with the exception of two, where the T wave was not affected; the average decrease was 1.6 mm., or 1.2 mm. per ten beat increase of heart rate. Since the decrease after infusion of atropine was only 0.4 mm. per ten beats, it follows that epinephrine exerts a marked specific effect on the T wave beyond the effect of the tachycardia caused by its administration. Decrease in the amplitude of the T wave was usually accompanied by a characteristic earlier appearance of its apex (Fig. 5). Inversion of the T wave affected lead II in two persons and lead V_4 in two others; the T waves of these persons at rest were low (less than 2.5 mm. compared to an average of 4 mm. in the athletes and 3.1 mm. in the non-athletes) and the increase of heart rate was considerable. After atropine was given, epinephrine administration caused a decrease in amplitude of the T wave in twenty, no change in four and an increase in fifteen; the average change was a decrease of 0.4 mm. corresponding to a decrease of 0.3 mm. per ten beat increase of heart rate. As in the young women, increase of the T wave was usually accompanied by superposition of a U wave on the T wave. Inversion of the T wave in lead II appeared in seven subjects. This higher incidence of inversion of the T wave can be explained by the fact that the T waves were already very low as a result of tachycardia caused by atropine (Fig. 5).

S-T SEGMENT

Infusion of norepinephrine did not cause any appreciable depression of the S-T segment even if the T wave became inverted. On the other hand, infusion of epinephrine was characterized by a horizontal and finally a descending

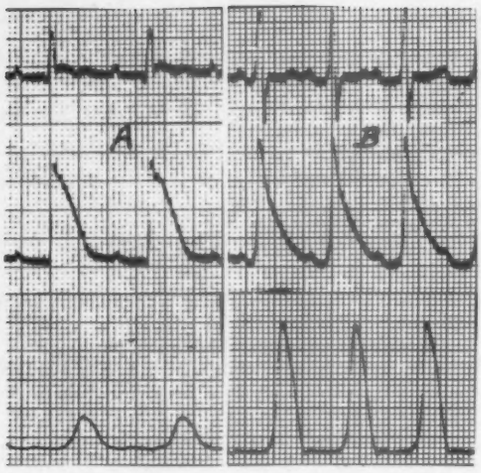

FIG. 6. Direct unipolar electrocardiogram from the left ventricle, monophasic action potential registered with the suction electrode and intraventricular pressure of an isolated, perfused rabbit heart. A, normal Krebs-Henseleit solution. B, after addition of epinephrine. A ventricular ectopic rhythm with complete A-V dissociation is present. (From an experiment of E. Lepeschkin, B. Surawicz and H. C. Herrlich.)

course of the S-T segment which became a direct continuation of the depressed P-R segment and showed a direct transition into the negative phase of a diphasic and finally inverted T wave. In most subjects the S-T depression was accordingly "false,"[10] and was caused on the one hand by continuation of a negative atrial T wave into the S-T segment, on the other hand by superposition of an elevated U wave on the P wave, which made determination of the true baseline impossible. This type of S-T segment depression appeared in almost all the young men when epinephrine was infused after atropine, leading to marked tachycardia (Fig. 5). However, in subjects in whom the 0.3 μg. dose of epinephrine led to bradycardia the S-T segment became depressed during its initial portion also with reference to the continuation of the P-R segment into QRS (Fig. 3). The depression of the S-T segment was most pronounced in leads which had tall R waves (usually I, V_4, V_5 and V_6).

U WAVE

Norepinephrine administration caused a slight elevation of the U waves, such as has been found under all circumstances which cause a slowing of the heart,[11] but did not change its usual time of appearance after the T wave[12] or its configuration. The 0.1 μg. dose of epinephrine caused definite elevation of the U wave, which showed an earlier beginning and summit but usually remained well separated from the T wave. The higher doses of epinephrine in the young women caused the U wave not only to become elevated, but also to show at first partial, then complete fusion with the T wave. When fusion was partial, the T-U junction was elevated, but could be easily recognized (Fig. 3). When fusion was complete, the U wave looked like a tall, wide T wave, and only the presence of a notch or kink in the ascending branch of this "combination wave"[13] indicated the boundary between the two waves (Fig. 4). As mentioned before, the second sound always coincided with this notch or kink. Although the apex of the U wave showed an earlier beginning, its duration was also increased so that its descending branch filled out the entire diastolic interval, even at low heart rates, as an "after-potential."

The amplitude of the U wave was measured from its apex to the point where its descending branch approached a horizontal line; if the P-R segment appeared to form a direct continuation of this branch, the beginning of the QRS complex was taken as the baseline. The amplitude of the U wave, measured in this way, accordingly included the slow terminal portion of the U wave designated by Sjöstrand as a "positive after-potential."[14,15] As the U wave was thought to originate partly from after-potentials connected with myocardial contraction and relaxation,[16–18] the increase in the amplitude of the U wave in lead V_4 after infusion of epinephrine in the forty young men was correlated with the increase in the difference between systolic and diastolic pressures, which can be considered as a rough measure of the amplitude of cardiac contraction. In subjects showing more than 0.5 mm. elevation of the U wave this difference showed a mean increase of 5.16 mm. while in those showing a smaller elevation of the U wave this difference was 4.02 mm. However, this difference was not significant statistically since the scatter of the individual values was very great. In the sixty young women the increase of amplitude of the U wave was plotted against heart rate and systolic blood pressure as in Figure 1. No definite dependence on these values could be observed, but the U wave was always higher with the higher dose of epinephrine.

COMMENTS

The configuration of the ventricular complex of the electrocardiogram appearing after ad-

ministration of epinephrine is characterized by lower voltage of the T wave, earlier appearance of its apex, and finally, diphasic configuration of the T wave with a short descending S-T segment; at the same time, diastolic voltages appearing at the time of the U wave are increased. The decreased voltage of the T wave is the usual finding with smaller doses[5] while inversion of the T wave followed by a huge U wave does not appear unless higher doses are given, especially by intravenous injection.[14]

Changes in Repolarization Phase: The change in the ventricular action potential responsible for these electrocardiographic changes are illustrated in Figure 6. They consist of a shorter and steeper course of the initial repolarization phase (plateau or phase 2), accompanied by a slowing of the terminal repolarization phase until it extends far into diastole as an "after-potential." While the fastest rate of repolarization normally takes place at the end of the action potential, epinephrine administration causes repolarization to occur most rapidly soon after the beginning of the action potential. As in the normal heart, relaxation after epinephrine is given seems to be initiated as soon as repolarization reaches a certain critical level, and this accounts for our observation that the second heart sound, as well as the beginning of the descending branch of the intraventricular pressure in Figure 5, appears earlier. The faster initial repolarization leads to the condition that at the end of QRS parts of the ventricle which were activated earliest are already partly repolarized, while the portions activated latest are still fully depolarized. This causes a displacement of the S-T segment opposite the main area of QRS; this displacement is greatest in leads with tall R waves and at high heart rates, which leads to further acceleration of repolarization. The same factors result in a decrease in the ventricular gradient[22] and a tendency of the T wave to be displaced more in a direction opposite to the QRS area.[5] The increased systolic rotation of the heart can account for only the initial T wave changes.[22] On the other hand, the increased duration of the terminal repolarization phase would accentuate the local differences in the degree of final repolarization and lead to tall positive U waves.

Although we have referred to the potentials produced during residual diastolic depolarization as U waves, it is probably more correct to call them "after-potentials" on which the original U waves are superimposed, in the terminology of Cannon and Sjöstrand.[14] It appears probable that the normally occurring U waves are related to mechanical activity of the heart[16–18] and have accordingly a different significance. This interpretation is confirmed by our failure to find a definite relation between the amplitudes of the diastolic potentials appearing after epinephrine administration and the pulse pressure.

Role of Potassium: Almost identical changes of the ventricular complex appear in hypopotassemia.[19,20] On the other hand, the typical electrocardiographic changes produced by administration of epinephrine can be suppressed by administration of potassium.[14,15] It is probable that epinephrine acts by increasing the speed of ionic transport through the cell membrane, including that of the exit of potassium which is responsible for repolarization,[21] and this would explain the increased initial speed of repolarization which leads to the characteristic T wave changes. At any rate, it is clinically important that under the influence of epinephrine or hypopotassemia an abnormal configuration of the ventricular complex which would otherwise be suggestive of coronary insufficiency may appear without any clinical symptoms of this condition, and in healthy young women in whom coronary disease is very unlikely.

Ectopic Rhythms: The effect of epinephrine in facilitating ectopic rhythms is due to its tendency to increase the speed of spontaneous diastolic depolarization which is characteristic of the specific conduction system. This depolarization, which is the basis of rhythmic stimulus formation, may even appear in fibers, which previously did not show it.[21,26] This effect can be explained by an acceleration of ionic transport across the cell membrane since the diastolic depolarization is ascribed to gradual entry of sodium into the cell.[21] The same mechanism is responsible also for the increase in the rate of normal sinus rhythm.

Sympathetic and Vagal Tone; Atropinization: A difficult question is whether or not the difference between the effects of epinephrine and norepinephrine on the heart can be explained entirely by the considerably greater vasoconstrictive and hypertensive action of norepinephrine, which leads to a reflex increase in vagal tone and a decrease of sympathetic tone originating in the pressoreceptor areas.

In atropinized cats the effects of these substances on the electrocardiogram and heart rate were almost identical, although the ectopic rhythms were more common with epinephrine.[3-6] Although during infusions of equal doses of epinephrine and norepinephrine the heart rate was considerably lower in the latter case, even at equal systolic blood pressures, this could have been due to the much greater increase of diastolic pressure in the case of norepinephrine. In the young men of our series the changes of heart rate and T waves caused by administration of norepinephrine after atropine was given were similar to those caused by infusion of epinephrine without atropine, and this has been reported by other workers.[23] However, after atropine was given, epinephrine administration still caused greater changes than norepinephrine. It is probable that even when the increase in vagal tone caused by the hypertensive effect of norepinephrine is abolished by administration of atropine, the decrease in sympathetic tone caused by this effect remains and is sufficient to partly counteract the direct effect of norepinephrine on the heart. In the isolated heart norepinephrine was found to have the same effect as epinephrine on electrocardiogram and excitability,[24] although the effect on heart rate was smaller,[25] and the effect of norepinephrine in lowering the diastolic excitability threshold was even greater than that of epinephrine.[26]

Summary

Electrocardiograms were registered during infusions of epinephrine and norepinephrine, 0.2 to 0.3 μg. per kg. per minute, in 100 normal young adults. Epinephrine caused increase of heart rate (a decrease occurred when the hypertensive effect was great), lower voltage of the T wave, elevation and earlier appearance of the U wave, and depression of the S-T segment. Inversion of the T wave in lead II and sometimes also in leads V_4 to V_6 occurred in about 10 per cent of the subjects, while in about 10 per cent the elevated U waves showed fusion with the T waves, resulting in a combination wave which resembled a wide, elevated T wave. This effect is explained on the basis of change in repolarization velocity seen in ventricular action potentials. Norepinephrine infusion caused decrease of heart rate and usually elevation of the T wave, but after atropine was given its effect became similar to that of epinephrine. Ectopic rhythms appeared after norepinephrine administration only at high blood pressure levels and at low heart rates, while after epinephrine administration they appeared at all rates. The differences between the effects of these two substances are attributed largely to partial counteraction of the direct effect of norepinephrine on the heart by reflex vagal excitation and sympathetic inhibition originating in the pressoreceptor areas.

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The Adrenosympathetic and Adrenocortical Function in Cardiac Insufficiency*

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In view of the powerful influences exerted by the adrenosympathetic catecholamines, epinephrine and norepinephrine, on cardiac metabolism and dynamics, on the one hand, and of adrenal corticoids on electrolyte and water balance, on the other, it appeared of interest to investigate the quantitative behavior of some of these neurohormones and hormones in patients with cardiac insufficiency.[1] We expected to obtain from these studies some clues regarding the degrees of both adrenosympathetic and adrenocortical activity in connection with cardiac insufficiency and regarding their mutual relations,[1] as after operations[2–4] and examinations.[5]

A close similarity has been reported between the metabolic alterations of the heart muscle occurring after the administration of adrenaline, and those found in failing human hearts.[6] These observations and the injurious effects of catecholamine injections and of catecholamine discharges under stress on the structure of the heart muscle[7,8] suggested a possible participation of local myocardial catecholamine action in the mechanism of cardiac failure. However, investigations concerning the concentration of epinephrine, norepinephrine and total catecholamines in the heart muscle of persons who had died in congestive heart failure did not provide any conclusive data.[9,10] Thus, although some indirect indications of a possible involvement of adrenosympathetic catecholamine overactivity in clinical cases of heart failure seem to exist, direct evidence is still missing.

More positive data are available concerning an augmented secretion of adrenal mineralocorticoids in connection with heart failure. Overdosage of desoxycorticosterone acetate produces signs of congestive heart failure,[11–13] and this condition also occurs not infrequently in the terminal stages of hyperadrenocorticism (Cushing's syndrome).[1] A participation of sodium- and water-retaining mineralocorticoids in the edema of patients with heart disease is suggested by the diminished excretion of sodium in the urine,[14–16] in thermal sweat[17,18] and in the saliva,[19] and by an augmented urinary excretion of aldosterone.[14,15,20–25] The latter has been interpreted as a secondary feature in established heart failure.[29] In some patients with cardiac insufficiency, the excretion of glucocorticoids was also found to be increased,[30] possibly as a result of general stress and anoxia.[31] The excretion of 11-oxysteroids[30,32–34] and of 17-ketosteroids was found diminished in severely decompensated patients with heart disease. The excretion and plasma levels of 17-hydroxycorticosteroids were, likewise, low in acute cases[33] and the ACTH test produced only small corticoid augmentations.[32] Some patients with severe decompensation display a good diuretic response to the administration of corticoids.[35,36] An actual deficiency of adrenocorticoid function in decompensated patients and those resistant to therapy is suggested by a reduced lipid and cholesterol ester content of the adrenal cortex at autopsy,[1,33,37] whereas in patients with compensated cardiac insufficiency the cortical lipids were found to be increased.[37] Excellent therapeutic results have been achieved in some patients with severe congestive heart failure by combined subtotal adrenalectomy and sympathectomy.[38]

Material and Methods

The excretion of norepinephrine, epinephrine, 17-hydroxycorticosteroids and 17-ketosteroids in the urine and the content and diurnal rhythm of the free and conjugated 17-hydroxycorticosteroids in the plasma were determined in 120 patients. Of this

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TABLE I
Grouping of Patients According to Age and Sex

Age (yr.)	Number of Patients		
	Total	Men	Women
40	8	6	2
41–50	13	10	3
51–60	29	19	10
61–70	34	17	17
71–90	36	17	19
Total	120	69	51

TABLE II
Grouping of Patients According to Degree of Cardiac Insufficiency

Group	No. of Patients
I	27
II	38
III	24
IV	20
V	11
Total	120

number, there were seventy-eight patients with myocardial degeneration, twenty-five with rheumatic heart disease and seventeen with chronic cor pulmonale. Patients in whom there were no complications, e.g., of renal origin, were chosen. The patients were divided into five groups according to the degree of cardiac insufficiency and the clinical signs: *Group I, mild insufficiency:* The liver was enlarged by 1.5 cm. There was some edema of the feet, which responded well to digitalis therapy. *Group II, moderate insufficiency:* Dyspnea appeared on slight effort. The liver was enlarged by 1.5 to 3 cm. below the costal margin. Administration of diuretic agents was required. *Group III, medium insufficiency:* The liver was enlarged by 3 to 4.5 cm. and there was definite congestion of the lungs. Weight loss under treatment amounted to 4 to 5 kg. *Group IV, severe insufficiency:* There was marked dyspnea at rest and definite cyanosis and edema, with a weight loss of 5 to 10 kg. after treatment. Sometimes there was fluid in the pleural cavity. The liver was enlarged by 4.5 to 6 cm. *Group V, very severe insufficiency:* There was very pronounced edema, often anasarca and marked dyspnea. Generally these patients responded poorly to therapy. Often a mechanical evacuation of fluid was necessary. The distribution of the patients according to age, sex and degree of heart insufficiency is shown in Tables I and II.

TABLE III
Urinary Excretion of Epinephrine and Norepinephrine in Patients with Cardiac Insufficiency During the First Hospital Day

Group	Epinephrine		Norepinephrine	
	μg./24 hr.	No. of Patients	μg./24 hr.	No. of Patients
I	5.0 ± 2.1*	14	19.0 ± 5.3	21
II	7.1 ± 2.5	17	16.9 ± 2.6	31
III	11.7 ± 3.1	10	20.7 ± 3.8	16
IV	7.8 ± 1.3	11	17.9 ± 5.0	17
V	1.9 ± 0.6	7	20.5 ± 4.5	9
Average	7.0	59†	18.5	94†

* Standard error of the mean.
† These figures represent totals

The levels of epinephrine and norepinephrine in the urine were determined using aluminum oxide absorption at pH 8.5, sulfuric acid elution and precipitation of salt by alcohol-acetone solution.[2,39–41] Epinephrine was assayed by the hen's rectal cecum method and norepinephrine by the cat's blood pressure method.[2,5,39] The total 17-hydroxycorticosteroids in the urine were determined by the method of Jenkins and others[2,3,42,43] using the butanol extraction and the Porter-Silber phenylhydrizine-sulfuric acid color reaction. 17-Ketosteroids were determined by a modification of the methods of Zimmermann and Callow.[2,42] Control data on total 17-hydroxycorticosteroids and 17-ketosteroids in the urine have been published earlier.[2,3,42] The free and conjugated 17-hydroxycorticosteroids in plasma were determined by the method of Peterson and Wyngaarden.[44–46] The accuracy of the steroid determination has been evaluated previously.[42]

RESULTS

Excretion of Epinephrine: During the first hospital day the average excretion was 7 μg. (in fifty-nine patients), which can be considered nearly normal, with indications of a slight activation of the function of the adrenal medulla (the normal was 5.2 μg. in medical students and 4.4 μg. in patients before surgery[2,5]) (Table III). In one-fourth of fourteen patients with cardiac insufficiency the amounts were increased above 10 μg. The highest excretion of epinephrine was 36.1 μg. in a patient with cor pulmonale and severe cyanosis. In more than half the patients with cardiac insufficiency the excretion was under 5 μg. In patients in group III (medium insufficiency) a distinct rise in the average

TABLE IV

Urinary Excretion of Epinephrine and Norepinephrine* in Patients with Cardiac Insufficiency

Group and No. of Patients	Hospital Day			
	1	2	3	7
	Epinephrine			
I, 26	5.7 ± 1.2†	3.9 ± 0.8	3.2 ± 1.7	...
II, 9	7.2 ± 2.4	...	...	7.9 ± 2.2
	Norepinephrine			
I, 42	16.6 ± 2.1	14.4 ± 2.2	12.4 ± 1.7	...
II, 25	18.0 ± 3.5	...	...	20.5 ± 4.5

* μg./twenty-four hours.
† Standard error of the mean.

excretion of epinephrine was noted (11.7 μg.), while on the other hand, those in group V (most severe insufficiency) showed a low excretion (1.9 μg.), which suggests either a decrease in the production caused by exhaustion or an impaired excretion mechanism. An increased excretion of epinephrine in individual patients appeared in 45 per cent of those with moderate to severe insufficiency (groups II, III and IV), but in only 10 per cent of those with mild and severe insufficiency (groups I and V). Only few patients showed increased excretion on the second and third day or after one week (Table IV). The treatment for heart failure had no significant effect on the excretion of epinephrine.

Excretion of Norepinephrine: On the first hospital day the mean excretion of norepinephrine was 18.5 μg. (in ninety-four patients) (Table III), which does not differ from the normal excretion of medical students (17.9 μg.) or of patients before surgery (24.3 μg.).[2,5] Excretions above 30 μg. during the first hospital day occurred in only 14 per cent. In 7 per cent the excretion was moderately increased, e.g., over 50 μg. The highest excretion of norepinephrine was 90.7 μg. Excretions less than 20 μg. were found in two-thirds of the total number of patients. There were no differences in the average excretion among patients with different degrees of cardiac insufficiency. There was no obvious decrease in excretion immediately after treatment or after one week (Table IV).

TABLE V

Urinary Excretion of 17-Ketosteroids and Total 17-Hydroxycorticosteroids in Patients with Cardiac Insufficiency During the First Hospital Day

Group	17-Ketosteroids		17-Hydroxy-corticosteroids	
	mg./24 hr.	No. of Patients	mg./24 hr.	No. of Patients
I	6.4 ± 1.4*	19	8.2 ± 2.3	25
II	5.2 ± 1.0	28	5.3 ± 0.8	37
III	6.2 ± 2.2	16	8.0 ± 2.1	19
IV	4.1 ± 1.0	17	4.0 ± 0.8	17
V	3.5 ± 0.9	9	6.7 ± 1.4	9
Average	5.2	89†	5.9	107†

* Standard error of the mean.
† These figures represent totals.

Excretion of Total 17-Hydroxycorticosteroids and 17-Ketosteroids: During the first hospital day, the average excretion of total 17-hydroxycorticosteroids was 5.9 mg. (in 107 patients), and of 17-ketosteroids 5.2 mg. (in eighty-nine patients), which for patients in this age group can be considered as nearly normal (Table V). The highest average excretion of total 17-hydroxycorticosteroids was 46.8 mg. in a patient with cardiac insufficiency (Table VI). No retention of free or conjugated 17-hydroxycorticosteroids was observed in his plasma, but the excretion of epinephrine was several times the normal levels. The highest excretion of 17-ketosteroids

TABLE VI

Distribution of the Urinary Excretion of 17-Ketosteroids and Total 17-Hydroxycorticosteroids in Patients with Cardiac Insufficiency During the First Hospital Day

Excretion (mg./24 hr.)	17-Ketosteroids (No. of Patients)	17-Hydroxy-corticosteroids (No. of Patients)
<2	27	27
2–5	31	35
5–10	21	28
10–15	5	12
15–20	1	1
>20	4	4
Total	89	107

TABLE VII

Correlation Between the Urinary Excretion of Total 17-Hydroxycorticosteroids and the Content of Free 17-Hydroxycorticosteroids in the Plasma of Patients with Cardiac Insufficiency During the First Hospital Day

No. of Patients	Morning Content of Free 17-Hydroxy-corticosteroids (μg. %)	Excretion of Total 17-Hydroxy-corticosteroids (mg./24 hr.)
3	<10	1.5
37	10–20	4.1
45	20–30	7.5
8	>30	6.6

was 39 mg. There was no correlation between the degree of cardiac insufficiency and the excretions of total 17-hydroxycorticosteroids and 17-ketosteroids, respectively. However, when the content of the free 17-hydroxycorticosteroids in the plasma was decreased, then the excretion of total 17-hydroxycorticosteroids in the urine was also decreased (Table VII). During treatment there was a slight tendency toward increase in the excretion of total 17-hydroxycorticosteroids (Table VIII).

No increase was observed in the excretion of 17-ketosteroids during treatment. In more than four-fifths of the patients the excretion was under 10 mg., and in more than half of the patients it was under 5 mg. (Table VI).

TABLE VIII

Urinary Excretion* of Total 17-Hydroxycorticosteroids and 17-Ketosteroids

Group and No. of Patients	Hospital Day			
	1	2	3	7
17-Hydroxycorticosteroids				
I, 25	4.5 ± 0.6†	7.0 ± 0.9	7.5 ± 0.8	...
II, 27	6.3 ± 1.5	...	...	7.6 ± 1.0
17-Ketosteroids				
I, 28	5.2 ± 0.7	7.1 ± 1.1	5.5 ± 0.8	...
II, 19	3.6 ± 1.8	...	...	5.6 ± 1.6

* Mg./twenty-four hours.
† Standard error of the mean

TABLE IX

Morning and Evening Plasma Concentrations of Free 17-Hydroxycorticosteroids in Patients with Cardiac Insufficiency During the First Hospital Day

Group and No. of Patients	Morning Content (μg. %)	Evening Content (μg. %)	Diurnal Rhythm (μg. %)
I, 26	21.1 ± 2.1*	11.9 ± 1.1	+9.2
II, 37	22.0 ± 1.0	17.6 ± 1.5	+4.4
III, 24	25.4 ± 1.5	21.3 ± 3.3	+4.1
IV, 19	24.9 ± 0.7	18.0 ± 1.0	+6.9
V, 10	23.7 ± 0.7	18.0 ± 2.1	+5.7
Average	23.1	17.2	+5.9

* Standard error of the mean.

Concentrations of Free 17-Hydroxycorticosteroids in Plasma: The mean content of the free 17-hydroxycorticosteroids in plasma was near normal in the morning (23.1 μg. per cent) and elevated in the evening (17.2 μg. per cent) during the first hospital day (Table IX). After one week it still remained somewhat elevated. The diurnal rhythm was therefore smaller than the normal average (7.4 μg. per cent).[4] Clearly augmented morning concentrations of free 17-hydroxycorticosteroids in the plasma were seen in a few patients (10 per cent). These levels were usually the same as in the control subjects (Table X). The evening concentrations were slightly increased in the patients with moderate to severe heart insufficiency (groups II, III, IV and V) with a clear decrease in the diurnal rhythm. Highest individual concentrations occurred in the morning (120.8 μg. per cent) and in the evening (90 μg. per cent). In the milder stage of insufficiency (group I) the average diurnal rhythm was almost normal (9.2 to 12.2 μg. per cent). A clear diminution was seen in other patients (group II, III, IV and V) (4.1 to 6.9 μg. per cent). In nineteen patients the diurnal rhythm of the free 17-hydroxycorticosteroids was reversed. Earlier we had found an evening retention of free and, especially, of conjugated 17-hydroxycorticosteroids in connection with renal insufficiency,[47,48] and a renal factor can be assumed to be present also in patients with cardiac insufficiency.

After one week's treatment the concentrations decreased slightly in the morning (1.9 μg. per

TABLE X

Distribution of Morning Content of Free and Conjugated Plasma 17-Hydroxycorticosteroids in Patients with Cardiac Insufficiency During the First Hospital Day

Free 17-Hydroxycorticosteroids (μg. %)	No. of Patients	%	Conjugated 17-Hydroxycorticosteroids (μg. %)	No. of Patients	%
<10	2	1.7	0–5	22	33.3
11–15	15	12.8	6–10	15	22.7
16–20	35	30.1	11–15	16	24.2
21–25	33	28.5	16–20	14	21.2
26–30	19	16.3	21–25	8	12.1
31–40	7	6.0	26–30	3	4.5
>40	5	4.3	30	8	12.1

cent) and in the evening (2.8 μg. per cent) (Table XI). The content of free 17-hydroxycorticosteroids in the plasma and the diurnal rhythm were highest when weight loss was from 5 to 10 kg. during the period of therapy (Table XII).

Concentrations of Conjugated 17-Hydroxycorticosteroids in Plasma: During the first hospital day the mean concentrations of conjugated 17-hydroxycorticosteroids in the plasma were nearly normal in the morning (16 μg. per cent) (in eighty-seven patients) and in the evening (12.8 μg. per cent) (Table XIII). The diurnal rhythm (+2.9 μg. per cent) was somewhat low. In 14 per cent of the patients, concentrations increased over 30 μg. per cent. In 46 per cent of the patients, the content was less than 10 μg. per cent, and in one-third of the patients the morning content remained under 5 μg. per cent (Table X), indicating a deficient conjugation. By contrast, the content of the free 17-hydroxycorticosteroids was extremely low in only two patients. In patients with the most severe cardiac insufficiency (group V), there were low concentrations of conjugated 17-hydroxycorticosteroids in the morning and in the evening (average 5.3 and 7.1 μg. per cent, respectively). The highest average content was found in patients of group III.

Treatment had a normalizing effect on the content of 17-hydroxycorticosteroids in the plasma. On an average, treatment did not affect the conjugated 17-hydroxycorticosteroid levels in plasma (the decrease of the morning concentrations was 3.5 μg. per cent and that of the evening 0.6 μg. per cent) (Table XI). Obviously the mild retention in a few patients and the deficiency of conjugation were abolished

TABLE XI

Effect of Treatment on the Free (Forty Patients) and Conjugated (Thirty Patients) 17-Hydroxycorticosteroids Plasma Concentrations in Patients with Cardiac Insufficiency

Time	Free 17-Hydroxycorticosteroids (μg. %)		Conjugated 17-Hydroxycorticosteroids (μg. %)	
	Morning	Evening	Morning	Evening
First hospital day	24.0 ± 1.6*	18.9 ± 1.6	14.4 ± 2.8	14.9 ± 4.7
After one week	22.1 ± 1.6	16.1 ± 1.1	10.9 ± 1.6	14.3 ± 2.2
Difference	−1.9	−2.8	−3.5	−0.6

* Standard error of the mean.

TABLE XII

Correlation Between Weight Loss During the Treatment of Patients with Cardiac Insufficiency and Morning and Evening Contents of Free 17-Hydroxycorticosteroids in the Plasma During the First Hospital Day

Weight Loss (kg.) and No. of Patients	Content of Free 17-Hydroxycorticosteroids (μg. %)		
	Morning	Evening	Diurnal Rhythm
<2, 31	18.8	14.5	+4.3
2–5, 41	23.4	17.0	+6.4
5–10, 26	26.6	18.7	+7.9
>10, 11	22.9	17.1	+5.8

TABLE XIII
Morning and Evening Concentration of Conjugated 17-Hydroxycorticosteroids in Patients with Cardiac Insufficiency During the First Hospital Day

Group and No. of Patients	Morning Content (μg. %)	Evening Content (μg. %)	Diurnal Rhythm (μg. %)
I, 17	17.2 ± 2.8*	13.7 ± 3.5	+3.5
II, 28	13.2 ± 1.9	12.0 ± 2.0	+1.2
III, 20	23.3 ± 8.6	16.0 ± 2.3	+6.3
IV, 13	16.6 ± 6.3	12.7 ± 3.4	+3.9
V, 9	5.3 ± 2.1	7.1 ± 1.9	−1.8
Average	16.0	12.8	+2.9

* Standard error of the mean.

after treatment. In patients with a slight increase of conjugated 17-hydroxycorticosteroids in the plasma there was an obvious decrease after a week's treatment.

COMMENTS

Catecholamines in the Urine: A slight average increase of excretion of epinephrine (7.1 μg.) was found in the urine of patients with cardiac insufficiency, especially in those with medium insufficiency (group III, 11.7 μg.). The average excretion of epinephrine was smallest in those with very severe insufficiency (group V, 1.9 μg). Excretion of norepinephrine was about normal (average 18.5 μg.) with only a few exceptions.

In some instances, the excretion of epinephrine was quite distinctly augmented but still to a lesser degree than in normal subjects after surgery (average 13.5 μg.)[2] or in students during the emotional tension preceding and during an examination (average 22.3 μg.).[5] After surgery, the excretion of norepinephrine was, likewise, markedly increased (average 59.1 μg.)[2] in contrast to the normal values found in cardiac insufficiency. In patients with acute myocardial infarction, augmented amounts of epinephrine and norepinephrine have been observed in the urine[39,49] and plasma[50,51] but this represents a different situation.

No clear correlation could be detected between individual elevated urinary excretion of epinephrine and the etiology, symptomatology, effectiveness of treatment and prognosis of the respective cases of cardiac insufficiency. The mechanisms responsible for exaggerated secretion of epinephrine in some of our patients are not identified, but the stress of general hypoxia[31] may be suspected as being involved. Of course, no information can be expected from studies on urinary excretion concerning sympathogenic intramyocardial catecholamine discharges and the local catecholamine metabolism within the failing heart muscle.

17-Hydroxycorticosteroids: Averages of conjugated 17-hydroxycorticosteroids in the plasma were lowest (5.5 μg. per cent in the morning and 7.1 μg. per cent in the evening) in the patients with most severe decompensation (group V). In another study[33] these corticoid levels have even been found to be below normal in patients with cardiac failure. The content of conjugated 17-hydroxycorticosteroids in plasma during the last months of pregnancy has been found to be relatively low,[52] but it has increased after surgery (33 μg. per cent).[4] In patients with hepatic disease there is a deficiency of 17-hydroxycorticosteroids.[53,54]

The plasma concentration and the urinary excretion of 17-hydroxycorticosteroids was above normal in only a few instances in contrast to the fourfold increase of total 17-hydroxycorticosteroids in urine (22.3 mg.)[2,3] and the twofold increase of free 17-hydroxycorticosteroids in plasma (41 μg. per cent) that had been observed after surgery[4] and during pregnancy (39.5 μg. per cent).[52] Thus, no generally distinct augmentation of cortical activity could be ascertained in our patients with heart disease.

Nevertheless, some importance may be attached to the fact that despite nearly normal morning values (23.1 μg. per cent), the evening concentrations of free 17-hydroxycorticosteroids in the plasma were increased to about twice the normal level (17.2 μg. per cent), which indicates a narrowing of the diurnal rhythm. A similar behavior has been observed in patients with renal disease,[47,48] except that in the latter, the conjugated 17-hydroxycorticosteroids in plasma are often markedly increased (69 μg. per cent) in correlation with the non-protein nitrogen and in inverse proportion to excretion of phenolsulphonphthalein.

Like the catecholamines, adrenal corticoids have been found by others[49,55] to be markedly increased in patients with myocardial infarction (both plasma levels and urinary excretion). The ratio corticosteroids:17-ketosteroids was augmented in such instances.[56]

17-Ketosteroids: The excretion of 17-ketosteroids in the urine was, on the average, slightly diminished (5.2 mg.). No correlation was

observed between the excretions of epinephrine, norepinephrine, 17-hydroxycorticosteroids, 17-ketosteroids and the urinary volume.

Our findings do not support the view that the adrenocortical steroids contribute significantly to the retention of sodium and water and to the formation of edema in patients with cardiac failure. The question arises as to whether or not the effect of steroids which retain sodium and water is sensitized by hemodynamic factors in patients with cardiac insufficiency.

Determinations of aldosterone, which other authors have found increased in cardiac failure, were not included in our studies.

Summary

Levels of epinephrine, norepinephrine, 17-ketosteroids and total 17-hydroxycorticosteroids were determined in the urine, and both free and conjugated 17-hydroxycorticosteroids in the plasma, in 120 patients with cardiac insufficiency of different degrees, according to which they were divided into five groups.

On the first hospital day, some patients gave assay values indicative of a distinct but transient adrenal medullary and cortical overactivity.

In about one-fourth of our patients the excretion of epinephrine was augmented, especially in patients with insufficiency of medium severity (possibly as a result of hypoxic stress), whereas excretion was lowest in patients with the most severe insufficiency.

Excretion of norepinephrine was augmented in only a few isolated instances. On an average it was within normal limits.

Except for a few elevated values, the free 17-hydroxycorticosteroids in the plasma were normal in the morning but approximately twice normal in the evening, indicative of a narrowed diurnal rhythm, especially in the patients with more severe insufficiency. This distribution remained fairly constant during the period of hospital observation.

Conjugated 17-hydroxycorticosteroids in the plasma were generally normal with a narrow diurnal rhythm. In patients with most severe insufficiency some elevated morning and evening values were observed. These tended to become normal with treatment.

The daily excretion of total 17-hydroxycorticosteroids in the urine was within normal range. 17-Ketosteroid excretion was low in accordance with the advanced age of most of the patients.

There was no clear quantitative relationship between the substances assayed and the etiology, symptomatology, urinary volume, effectiveness of treatment and prognosis of the respective cases.

Our results permit the assumption of a limited and temporary adrenal medullary overactivity in a minority of instances but they did not reveal any significant augmentation of adrenocortical activity in cardiac failure.

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Circulating Epinephrine and Norepinephrine in Coronary Occlusion*

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The literature contains several reports concerning tissue concentration and urinary excretion of catecholamines in coronary artery disease. Raab,[1] using a colorimetric method, reported an increase in blood levels of adrenergic amines in patients with angina pectoris after exercise. Nuzum and Bischoff[2] found increased amounts of epinephrine in the urine of two patients with myocardial infarction. Under similar conditions, however, Raab and Gigee[3] were unable to detect grossly abnormal urinary catecholamine excretion. The same authors[4] reported significant increases in epinephrine in human hearts at autopsy in subjects with recent myocardial infarction and in congestive heart failure. Bloodworth and von Haam,[5] on the other hand, found low or normal values under the same conditions.

Because of the variability of results in these reports and the availability of a quantitative method for amine determinations far more sensitive than those used by earlier investigators, a study has recently been made in this laboratory[6] on plasma concentrations of catecholamines in patients with myocardial infarction and angina pectoris. The results of this previous investigation revealed a significant increase in circulating norepinephrine in thirteen cases of myocardial infarction; in seven of these there was also a significant increase in epinephrine levels as compared to that found in normal subjects. There was a positive correlation of norepinephrine and transaminase levels, but there was no such relationship with epinephrine and transaminase. Furthermore, in twelve patients with angina pectoris, circulating norepinephrine increased in eight after mild exercise and epinephrine increased in five. In normal persons subjected to similar exercise, there was no significant change in plasma levels of catecholamines.[6] Recently, Starcich and Ambanelli[7] have observed increases in circulating catecholamines in coronary artery disease.

The present investigation was designed to measure and determine the source of the increments in plasma adrenergic amines following experimental coronary occlusion in dogs.

Methods

Coronary occlusion was accomplished either by the injection of glass microspheres into the coronary circulation or by ligation of the anterior descending coronary artery while the dog was under anesthesia with pentobarbital. Control blood samples for catecholamine analysis were drawn just prior to occlusion and at daily intervals for several days following occlusion.

In six preliminary experiments, circulating levels of catecholamines were determined at intervals for a period of about six hours following occlusion. Since no changes were noted in plasma concentrations during this period, all subsequent sampling was carried out at a longer interval following occlusion.

All blood samples were analyzed fluorimetrically according to our adaptation of the ethylenediamine condensation method.[8] The validity and usefulness of this method have been critically appraised recently by Manger, Wakim and Bollman.[9] In some instances, further decisive identification of the plasma constituents was obtained by fluorescence emission spectrums, as recorded by an Aminco-Bowman spectrophotofluorometer.

Serum transaminase values were determined in most instances. Arrhythmias and myocardial damage

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TABLE 1

Plasma Catecholamines (μg./L.) and Serum Transaminase (u./ml.) Before and After Acute Coronary Occlusion (mean values)

Time	Norepinephrine	Epinephrine	SGO-T
Normal Dogs (Thirty-Three)			
Control	1.6	0.3	40
Maximum values after occlusion	10.5*	0.2	251*
Adrenalectomized Dogs (Four)			
Control	1.6	0.2	30
Maximum values after occlusion	14.4†	0.2	210†
After 5 mg./kg. β TM10 Administered Intravenously (Six)			
Control	1.8	0.3	...
Values after occlusion and before administration of drug	9.4	0.1	...
10 minutes after administration of drug	3.9†	0.3	...
20 minutes after administration of drug	2.0‡	0.2	...
Dogs Given Reserpine (Eleven)			
Control	1.2	0.4	31
Maximum values after occlusion	10.1§	0.2	259*

* $p < 0.001$.
† $p < 0.05$.
‡ $p < 0.01$.
§ $p < 0.02$.

were assessed in all animals by means of electrocardiograms and pulse pressure curve tracings. In six dogs heart contractile force was measured directly.[10,11] At the end of each experiment the animal was examined postmortem and the cardiac lesions observed grossly.

In order to assess the role of the adrenal glands in response to coronary ligation, two-stage bilateral adrenalectomy was completed on four dogs several days prior to the ligation procedure. In another group of eighteen animals, reserpine was administered intramuscularly in a daily dose of 0.1 mg./kg. body weight on each of two days prior to ligating the artery. In six additional dogs, a sympatholytic agent, β TM10 (trimethyl-2-2,6- xylyloxy-propyl ammonium chloride monohydrate), was administered following coronary occlusion and during the subsequent period of elevated circulating norepinephrine. Finally, tissue analysis for catecholamines was performed in several instances on various sites in the damaged heart in an attempt to confirm or deny the theory that localized increments in tissue adrenergic amines contribute to the cardiac arrhythmias.[12]

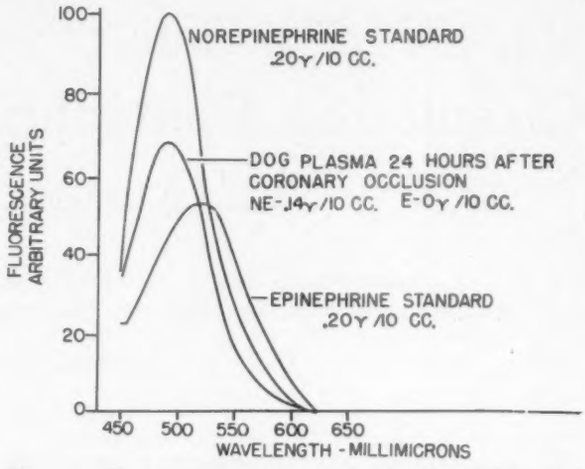

FIG. 1. Fluorescence spectrums of epinephrine and norepinephrine condensed with ethylenediamine (activation wave length, 436 mμ).

RESULTS

Composite results are shown in Table 1. In a group of thirty-nine dogs with occluded coronary arteries, five died within an hour after the procedure and one died within twenty-four hours. In the remaining thirty-three animals mean values of circulating norepinephrine increased maximally from 1.6 to 10.5 μg./L. of plasma ($p < 0.001$). In most instances, the maximum values were attained during the twenty-four- to thirty-six-hour interval following occlusion with a return close to control levels in forty-eight to seventy-two hours. Virtually no change occurred in circulating epinephrine. In most cases, there was a close parallelism in serum transaminase values and norepinephrine levels, the highest transaminase figures being recorded during the twenty-four- to thirty-six-hour interval when norepinephrine was maximally increased and subsiding in the forty-eight- to seventy-two-hour period. Elevated transaminase levels persisted somewhat longer than norepinephrine increments. At autopsy, gross examination revealed large infarcts in each heart.

Changes indicative of acute myocardial infarction were noted in all electrocardiograms and pulse pressure curve tracings and in the six animals in which myocardial contractility was measured.

TABLE II
Catecholamine Content of Left Ventricle (Mean Values in μg./gm.)

Data	No. of Hearts	Norepinephrine	Epinephrine
After coronary occlusion	3		
Core of infarct		0.28	0.02
Adjacent to infarct		0.68	0.02
Normal area		0.72	0.05
Normal hearts	5	1.18	0.06

In four bilaterally adrenalectomized dogs increases in plasma norepinephrine and in serum transaminase were in the same range as those in the normal dogs (Table I).

In six dogs following occlusion and the administration of β TM10, 5 mg./kg. body weight intravenously, progressive decline occurred in elevated circulating levels of norepinephrine. Twenty minutes after the injection of this choline ether, plasma catecholamines had returned to pre-occlusion levels (Table I).

In a group of eighteen animals, treated with reserpine, two died within an hour after the occlusive procedure and five others died within twenty-four hours. In the remaining eleven animals, virtually the same increases in norepinephrine and transaminase occurred as in the untreated dogs (Table I). The only difference was that in the animals given reserpine the maximum increases in plasma norepinephrine had a tendency to occur at a somewhat later time—in some instances seventy-two to ninety-six hours after occlusion.

Recordings of fluorescence emission spectrums afforded additional evidence identifying norepinephrine as the compound appearing in increased amounts in plasma following coronary ligation. Configuration of the plasma curve coincided almost exactly with that of authentic norepinephrine (Fig. 1). In several instances such recordings were used not only to aid in the identification of norepinephrine but also to serve as a confirmation of the circulating concentrations.

In three of the hearts with infarcts, no increases in catecholamine content were observed. Tissue from the infarcted area and immediately adjacent to it showed a somewhat lower concentration than normal cardiac tissue (Table II).

COMMENTS

The results of this study confirm and amplify those of our earlier reports on dogs[13] and on man.[6] In considering the significance of elevated circulating levels of norepinephrine in response to coronary occlusion it would appear that such a reaction possesses both beneficial and deleterious features. In the first instance, increased plasma levels of norepinephrine serve not only to maintain blood pressure through a pressor action but also to stimulate the myocardium directly.[14,15] In the absence of such a protective reaction, shock undoubtedly would occur more readily. Infusion of norepinephrine is one of the methods used for the management of shock secondary to myocardial infarction.[16] The useful effects produced by norepinephrine in response to coronary occlusion, however, may be modified by causing a waste of oxygen by the heart muscle that exceeds the simultaneous oxidative energy requirements for mechanical work.[17] Furthermore, excessively high circulating levels of catecholamines for prolonged periods in some instances have produced myocarditis, hemorrhagic lesions of the pericardium and endocardium and necrotizing endarteritis of the small bowel in experimental animals and in man.[18–20] The pathogenic significance of epinephrine and related substances in the heart muscle has been reviewed by Raab.[17,21] Such observations serve as an alert to the potential hazards involved in the prolonged use of massive quantities of catecholamines without deprecating their proper use when they are indicated. In the present investigation, it is doubtful that the elevation in circulating norepinephrine is sufficiently great or sustained for periods long enough to produce gross damage to the cardiovascular system. Further studies relating to this feature are in progress.

Source of Increased Circulating Norepinephrine: Our results suggest that the postganglionic adrenergic nerve endings are the chief source of the increased circulating levels of norepinephrine. The influence of β TM10, a choline ether, on the elevated norepinephrine plasma levels supports this hypothesis. Following the intravenous administration of this sympatholytic agent a progressive decline occurred in circulating levels of norepinephrine (Table I). Such agents abolish the effects of adrenergic nerve stimulation by preventing the output of norepinephrine without impairing conduction along adrenergic nerves. This suggests an action at or near the nerve terminals. In acute experi-

ments, the liberation of pressor amines from the stimulated adrenal glands is not affected by these choline ethers.[22]

Similar reductions in elevated plasma norepinephrine after occlusion were noted in three experiments with the ganglionic blocking agents hexamethonium (5 mg./kg.) and mecamylamine (1 mg./kg.) administered intravenously.

If the adrenal medullae were participating in the action, it would be reasonable to assume that increments in plasma epinephrine would occur in normal animals. Such was not the case (Table I). However, we have noted significant increases in epinephrine levels in seven of thirteen patients with acute myocardial infarction as compared to normal subjects.[6] Although the responses obtained in bilaterally adrenalectomized dogs were in the same range as those in normal dogs, this does not necessarily exclude the possibility that the adrenals contribute to the elevated plasma levels in the intact animal.

Reflex discharge of norepinephrine due to hypotension was eliminated since none of the animals showed signs of shock when blood samples were drawn for analysis.

Effect of Reserpine Therapy Prior to Occlusion: Since reserpine is known to deplete the norepinephrine stores of many tissues, the source of the substantial quantities of this amine present in plasma following coronary occlusion in dogs given reserpine is not readily apparent. Consideration should be given to the possibility that some of the normal sites of catecholamine storage are only partially depleted following the administration of reserpine. This is suggested by the fact that the degree of hypotension which follows treatment with reserpine is considerably less than would be expected to follow a complete blockage of sympathetic influence on the vascular bed. That the control level of norepinephrine in plasma of resting dogs remains easily detectable also indicates that complete depletion of catechols does not occur following the introduction of reserpine. Stimulation by nicotine of the adrenal medullas of dogs given reserpine results in significant increments in circulating norepinephrine and epinephrine.[23] The adrenals of some other species also exhibit only partial depletion. The innervated adrenals of cats have been shown to retain a substantial amine concentration following administration of reserpine. Furthermore, Kroneberg and Schümann[24] found that in rabbits the resting concentration of epinephrine in blood in the adrenal vein remained at 50 per cent of normal when the adrenals were largely exhausted by reserpine. Maling et al.[25] have recently reported that the adrenals of dogs given reserpine contain no norepinephrine. However, these authors found no measurable amounts of this amine in the medullae of normal dogs, while other investigators[26] have estimated norepinephrine to account for 18 to 52 per cent of the total adrenal catechols.

In the present study it is noteworthy that the mortality rate following coronary occlusion was higher (39 per cent) in the group of animals treated with reserpine than in the untreated group (15 per cent). Maling et al.[25] recently reported similar mortality rates for each group (about 14 per cent).

Catecholamine Content in Myocardium: Harris and Bisteni[12] have suggested that sympathoadrenal substances liberated during the necrosis of cardiac muscle may act as local excitatory factors to produce arrhythmias. We have shown previously that relatively large amounts of norepinephrine can be liberated from the isolated heart by appropriate stimulation with drugs.[27] However, in the present study there was no indication of localized increments of catecholamines in the myocardium. The norepinephrine content was actually less in the ischemic area than in the normal tissue (Table II). In no instance was the tissue concentration in the infarcted area elevated above the control value. These results are in agreement with those of Maling et al.[25] who have concluded from studies with reserpine and phenoxybenzamine in coronary occlusion that the release of norepinephrine from the infarcted area does not play a significant role in the development of arrhythmias. Furthermore, in our studies there was no apparent correlation of the plasma concentrations of adrenergic amines and the severity of the arrhythmias. In view of the avidity of the myocardium for injected epinephrine and norepinephrine,[28] it is surprising not to see elevated levels of catecholamines in the normal areas of the hearts with infarcts removed from animals at a time when circulating concentrations were above normal.

Fluorescence Spectrums: Additional evidence identifying norepinephrine in the plasma is afforded by recording of fluorescence emission spectrums (Fig. 1). Not only is this qualitative evidence for the presence of norepinephrine but in this instance it also constitutes a quanti-

tative analysis. The value of 0.14 μg. of norepinephrine in the dog plasma was obtained from calculations based on readings from another fluorimeter. By comparison of the height of this curve to that of the curve for the norepinephrine standard, good correlation is evident. These curves represent "apparent" fluorescence maximums and are not absolute values. As Hercules[20] has indicated, several factors, e.g., recorder-pen response and variation of detector sensitivity with wave-length, affect "true" fluorescence maximums. Although these are uncorrected curves, they do aid in the further identification and quantitation of norepinephrine.

It is suggested that the determination of plasma levels of catecholamines may be of use as a diagnostic aid in patients with coronary artery disease. Although the increments in plasma pressor amines seen in recent myocardial infarction and in angina pectoris following exercise do not reach the levels seen in pheochromocytoma, the moderate elevations can be measured readily and such determinations might serve a useful diagnostic purpose.

Summary

1. Following experimental coronary occlusion in thirty-nine dogs, mean values of norepinephrine increased maximally from 1.6 to 10.5 μg./L. of plasma in thirty-three surviving animals. Serum transaminase increments paralleled norepinephrine elevations in most instances. No changes occurred in circulating levels of epinephrine. Recordings of fluorescence emission spectrums aided in the identification and quantitation of the catecholamines.

2. Essentially the same results occurred in four chronically adrenalectomized dogs.

3. Following coronary occlusion and the administration of a sympatholytic agent (trimethyl-2-2,6 xylyloxy-propyl ammonium chloride monohydrate), elevated circulating levels of norepinephrine declined progressively to pre-occlusion figures.

4. Of eighteen dogs treated with reserpine, eleven survived the occlusive procedure and showed increments in norepinephrine and transaminase similar to those of the untreated animals.

5. The catecholamine content of the infarct and the adjacent area was not elevated above the values found in normal tissue.

Acknowledgment

We are obliged to Richard H. Gadsden, PH.D., Department of Biochemistry, for the serum transaminase determinations. We are also obliged to Mr. R. A. McLean, Smith Kline & French Laboratories for supplying the compound, β TM10 (trimethyl-2-2,6 xylyloxy-propyl ammonium chloride monohydrate).

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Pathologic Changes Induced by l-Norepinephrine

Quantitative Aspects*

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SOON AFTER adrenalin was synthesized, observations of its injurious effects began to accumulate. Some were incidental to therapeutic trials or poisoning; most of them, however, were planned experiments, as those of Josué,[1] Christian et al.,[2] Fleisher and Loeb,[3] Raab[4] and many others studying arterial and cardiorenal disease. Injury and reaction can be precipitated by both components of the "official epinephrine"; epinephrine proper and norepinephrine. The pathologic implications of the local and systemic lesions produced by these amines were the subject of a recent study from the U. S. Naval Medical School.[5]

"Norepinephrine myocarditis" in man following prolonged infusions of this pressor amine was described by Szakács and Cannon.[6] Similar lesions were observed by the same authors in patients suffering from pheochromocytoma and were produced in the dog by prolonged infusions of norepinephrine in amounts comparable to therapeutic dosages. Three additional patients with myocarditis attributed to excessive pressor amine therapy came to autopsy at this Center in the past six months. The cardiac lesions were morphologically identical in these three patients and they did not differ from the experimental lesions produced by norepinephrine in the dog, although the underlying basic disease was widely varied, from inhalation of smoke to contusion of the brain[7] and bronchogenic carcinoma. Basically, the lesions consisted of focal myocardial necrosis, inflammatory exudate and epicardial hemorrhage (Figs. 1 and 2). It is difficult to ascertain the frequency of this lesion at the present time. The largest group of patients treated with norepinephrine, those with myocardial infarction, have to be excluded from a survey since the lesions are difficult to differentiate from infarcts.

The therapeutic use of norepinephrine led to the universal observation that high doses of this pressor amine carry high mortality rates in the treatment of cardiogenic shock or shock-like states. This fact is important enough to be evaluated on a quantitative basis because it is easy to misinterpret the higher mortality rate as a result of the severity of the underlying disease and disregard the inherent toxicity of norepinephrine. Our earlier observations on l-norepinephrine myocarditis suggest that therapeutic doses possess such toxicity, and clinical observations by others suggest that more lives could be saved by *not* administering norepinephrine rather than by administering too much of the pressor agent[8] in the treatment of cardiogenic shock.

Cardiotoxicity is possessed by other pressor amines as well as by epinephrine and norepinephrine, although to a different degree. The comparative cardiac necrotizing activity of isoproterenol was studied by Chappel and his colleagues[9] on a quantitative basis employing single subcutaneous injections on two consecutive days. The lesions produced by the administration of the medial lethal dose, or its fractions, of isoproterenol were more severe compared to the administration of the same fractions of norepinephrine. The methods employed are reliable for the study of comparative

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The opinions or assertions contained herein are the private ones of the authors and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

FIG. 1. Myocarditis in a forty year old woman treated with l-norepinephrine for three days following inhalation of smoke. She died on the fourth day. Hematoxylin and eosin stain. Original magnification × 220.

toxicity of pressor amines although the single doses administered are necessarily high and not recommended in such form in current clinical practice. Since norepinephrine became the standard of reference for similar work, as well as a most popular therapeutic agent to keep within clinical application, its quantitative evaluation must be based on continuous prolonged infusions as recommended for treatment. It also must be comprehensive and correlate physiologic effects, pathologic changes, dosage rates and effective blood levels of catecholamines. From our experiments with infusions of graded doses of norepinephrine, it became evident that the time element, i.e., the duration of the infusion, is of primary importance. Dosages considered physiologic and indeed harmless, if administered for short periods of time, might become lethal during prolonged infusion. In this experiment only the smallest dose rate (0.5 μg. per minute per kg.) maintained the physiologic response characteristic of norepinephrine throughout the infusion period, i.e., bradycardia and elevation in mean blood pressure. Such responses changed and were even reversed with higher dosage rates.

MATERIALS AND METHODS

Twenty-eight male mongrel dogs weighing 9 to 18 kg. were sedated with morphine (2 mg. per kg.) and heparinized, using 2 mg. per kg. of crystalline U.S.P. heparin. One of the femoral arteries was catheterized and connected to either a direct reading mercury manometer or to a strain gage amplifier and recording apparatus. A polyethylene catheter was passed through a large superficial vein of the foreleg for the administration of norepinephrine (Levophed®) in 5 per cent dextrose in water. Electrocardiograms were taken at frequent intervals to determine the heart

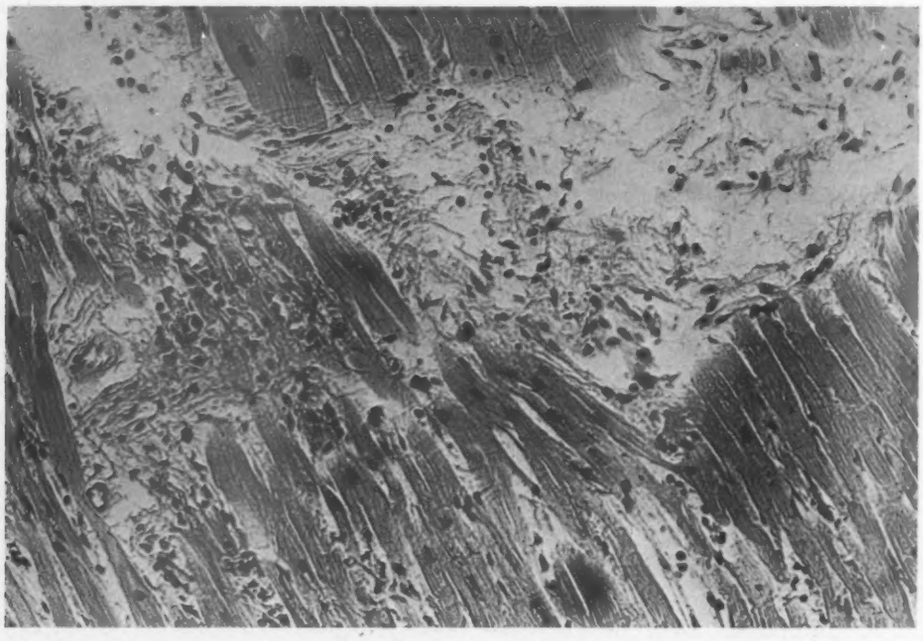

FIG. 2. Myocarditis in a forty year old woman with contusion of the brain. Hypotension developed thirty-two hours after the injury to the head. In the following six days she received a total of 202 mg. of l-norepinephrine base. Note myofibrillar necrosis (left of center), marked edema, polymorphonuclear exudate and cardiac histiocytes. Hematoxylin and eosin stain. Original magnification × 220.

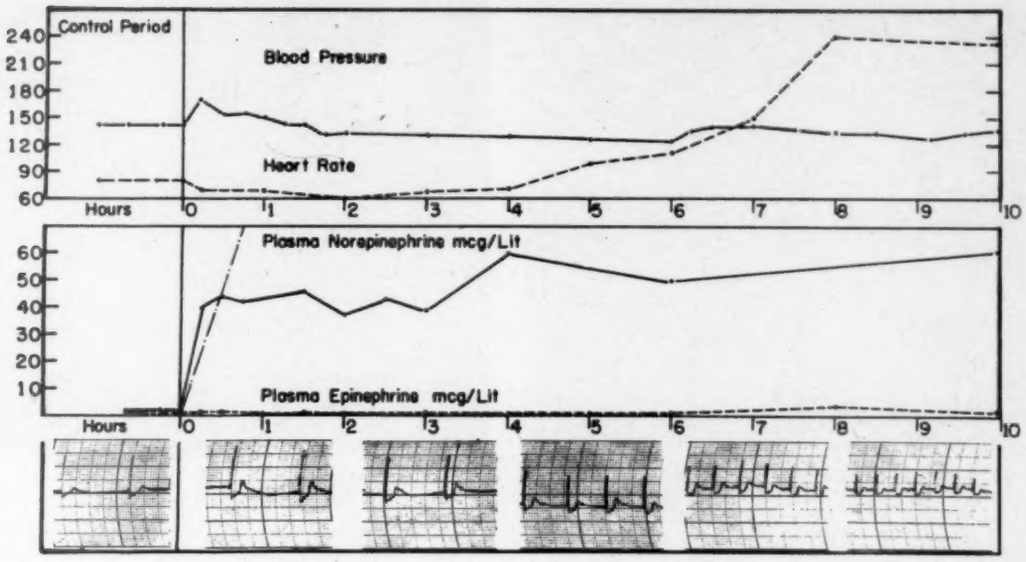

FIG. 3. Dog treated with norepinephrine 1.5 μg. per minute per kg. for ten hours. No gross pathologic changes developed in the heart.

rate and nature of the arrhythmias. The dosage rate, although constant in each individual experiment, varied between 0.5 to 15 μg. per minute per kg. expressed as l-norepinephrine base. Blood levels of epinephrine and norepinephrine were determined at given intervals up to ten hours in twelve animals. For these twelve animals a mechanically driven syringe was employed as a pump. In the other experiments a Sigma pump was utilized. Epinephrine and norepinephrine levels were determined by the fluorometric method of Weil-Malherbe and Bone.[10,11] The method was modified so as to utilize available equipment. The modifications have been previously reported.[12] Determinations of blood pH performed during the infusion period revealed a constant hydrogen ion concentration of 7.2 ± 0.1.

RESULTS

The two diagrams (Figs. 3 and 4) represent typical experiments in which doses comparable to those reported for therapeutic uses were employed. In the first one a normal dog was treated with 1.5 μg. per minute per kg. of norepinephrine for ten hours. For the first four-hour period the expected bradycardia and elevated mean blood pressure were present, but later a gradual increase of heart rate occurred

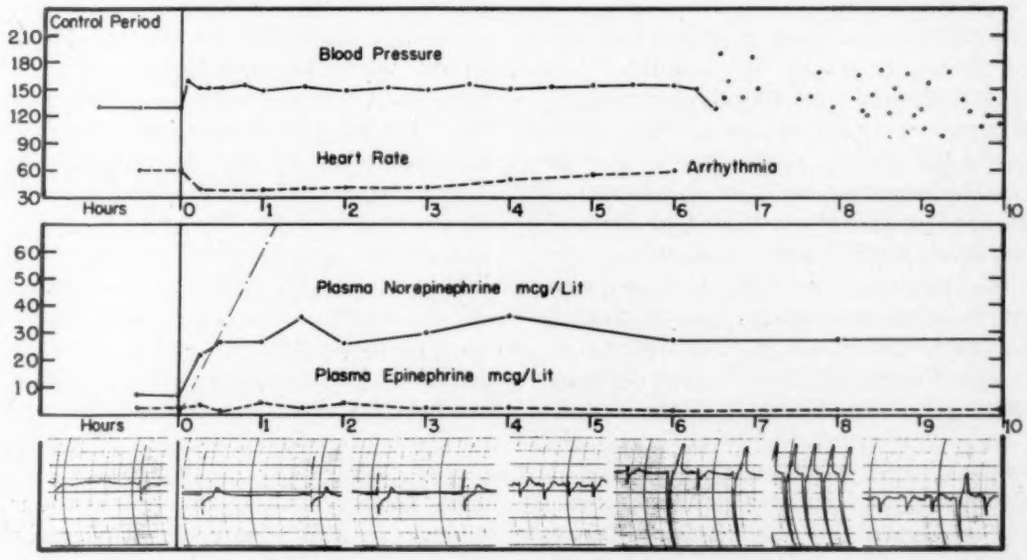

FIG. 4. Normal dog treated with norepinephrine 1 μg. per minute per kg. for ten hours. Gross pathologic changes developed in the myocardium.

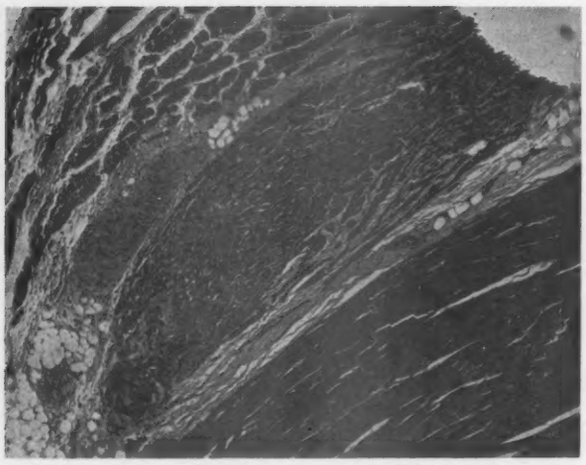

FIG. 5. Atrioventricular conduction bundle in a dog treated with norepinephrine 1.5 μg. per minute per kg. for twenty-six hours. Changes are not detectable with the hematoxylin and eosin stain. Original magnification × 120.

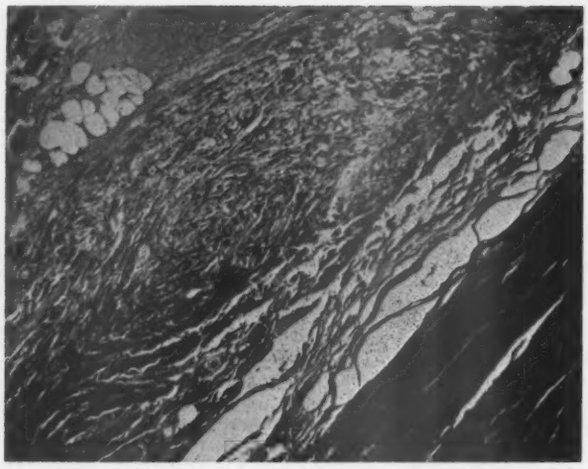

FIG. 6. Section from the same block of tissue as Figure 5, stained with acid fuchsin and photographed with a green filter. Black color represents fuchsinophilic degeneration in the conduction band and adjacent myocardium. Original magnification × 160.

without arrhythmia and the mean blood pressure fell a little below control levels. In this case the ten-hour period was not enough to produce gross pathologic changes in the heart, but for therapeutic purposes it is clear that the 1.5 μg. per minute per kg. would be useless in this animal in a condition requiring treatment for longer than four hours. The corresponding blood levels of norepinephrine show a fiftyfold increase in the first fifteen minutes and then stabilize, increasing only very slowly thereafter. No significant changes were present in the plasma epinephrine content.

The second diagram (Fig. 4) represents a dog treated with only 1 μg. per minute per kg. for ten hours. Severe cardiac arrhythmia, mainly ventricular tachycardia and ectopic beats developed after six hours in this animal. The blood pressure showed corresponding irregularities, and upon sacrifice of the animal, gross and microscopic lesions were present in the heart. In this second case a lesser amount of norepinephrine with only a thirtyfold increase in plasma level precipitated myocarditis, subendocardial hemorrhage and fuchsinophilic degeneration in the conduction system, emphasizing individual differences in susceptibility.

Morphologic Changes in Heart: To illustrate the morphologic changes in the heart and blood vessels, the conventional hematoxylin and eosin preparation should be first employed. It is true that early degenerative changes might not be demonstrated by this method, but it will enable us to differentiate genuine necrosis from degeneration of myofibrils still in a reversible state. This cannot be said about the acid fuchsin staining. Undoubtedly the fuchsinophilic fibrils are in some degree of degeneration and their function is probably impaired. However, only some of those fibrils become necrotic and invaded by inflammatory exudate, while others, if the nuclei survive, regenerate without scarring. This is in contrast with the assumption of Selye[13] who believes that "small particles of necrotic tissue can be absorbed without causing any discontinuity in the tissue, because the adjacent muscle fibers merely join together and fill the gap." In a previous paper[6] a single myofibril in a microscopic field that became necrotic under the influence of norepinephrine was illustrated. The reaction of this single fibril was the same as may be observed when large areas are affected. The fibril itself was discolored and fragmented and was invaded and surrounded by polymorphonuclear leukocytes and Anitschkow's myocytes. These latter cells have been interpreted as cardiac histiocytes by recent investigators. Histiocytes are followed by fibroblastic proliferation, and the end result is increased interstitial fibrosis. When a larger area is affected no qualitative difference exists, and the resultant scarring from such processes is well accepted.

The necrosis in the dog was usually accompanied by hemorrhage which helped to evaluate grossly the extent of the lesions. Fatty degeneration of the myocardium under the influence of high doses of norepinephrine was observed by Maling and Highman.[14] Both fatty change and fuchsinophilia are reversible

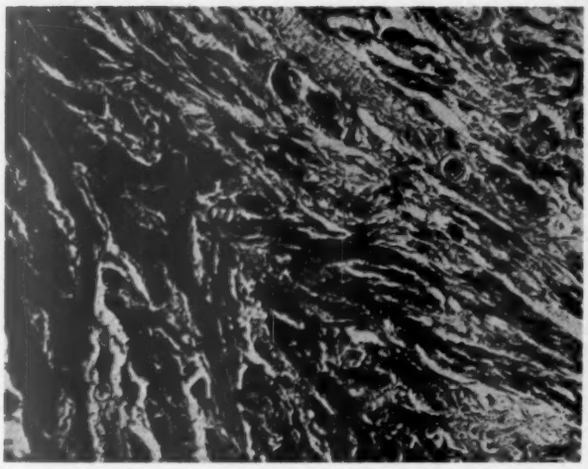

FIG. 7. High power view of the conduction bundle shown in Figure 6. Black color represents fuchsinophilic fibers. Acid fuchsin stain. Original magnification × 340.

morphologic changes in a functionally impaired heart prone to arrhythmia and especially to ventricular tachycardia. Branches of the coronary arteries and the arterioles often showed fibrinoid degeneration even in areas where necrosis of the myocardium was not apparent. The endocardial surfaces were more or less hemorrhagic and involved by a cellular exudate. The conduction system was subject to fuchsinophilic degeneration, but so far we have not been able to demonstrate inflammatory exudate in the nodes or bundles associated with cardiac arrhythmia. There is a close association between cardiac arrhythmias and gross pathologic changes (Figs. 5, 6 and 7). Capillary hemorrhages, especially in the subendocardium, are not difficult to explain, considering the prolonged periods of ventricular tachycardia which prevent capillary blood flow, at least in the subendocardial areas where the pressure gradient is the highest. In this central layer of the myocardium and in the papillary muscles the walls of the vessels become permeable under mounting oxygen debt and blood escapes into the surrounding tissues.

The lesions mentioned are characteristic in their development, in that they are produced by relatively low dosages (0.8 to 1.5 μg. per minute per kg.), if the infusion is prolonged enough, and they are independent of the mean blood pressure elevation. In some respects they are similar to diphtheritic myocarditis. Diphtheria toxin apparently is a bacterial cytochrome B able to compete with the intracellular cytochrome C of the host. The result is increasing hypoxia and ischemic necrosis in

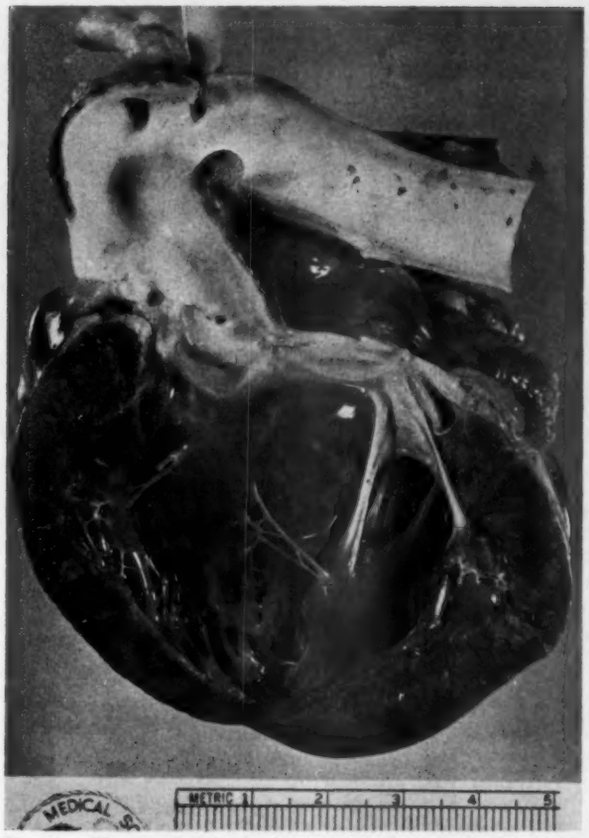

FIG. 8. Heart of a dog submitted to hemorrhagic shock for four hours and ten minutes, and treated with 1 μg. per minute per kg. of l-norepinephrine for the last three hours of the hypovolemic period. Blood pressure remained at 45 mm. Hg. The animal survived and was sacrificed twenty-one days later. Note the hemorrhagic medial necrosis of the aortic arch and minor subendocardial hemorrhage in the left ventricular wall.

some of the myofibrils.[15] Hypoxia, as proposed by Raab,[16] and loss of potassium may very well be the mechanism that produces norepinephrine myocarditis. With large doses, however, hemorrhagic manifestations become predominant both in the heart and other organs.

With administration of 10 to 15 μg. per minute per kg. of norepinephrine, the mean blood pressure suddenly rose above 300 mm. Hg. This pressure was able to rupture blood vessels and precipitate massive hemorrhages in the mitral valve, the roots of the great vessels, the brain and the lungs. The pathogenesis was clearly on a mechanical basis and the lesions reflected the extreme hemodynamic changes.

The aforementioned description sums up the morphologic changes that occurred in the cardiovascular system of the dog following administration of norepinephrine. In contrast to normal dogs, if those in hemorrhagic shock

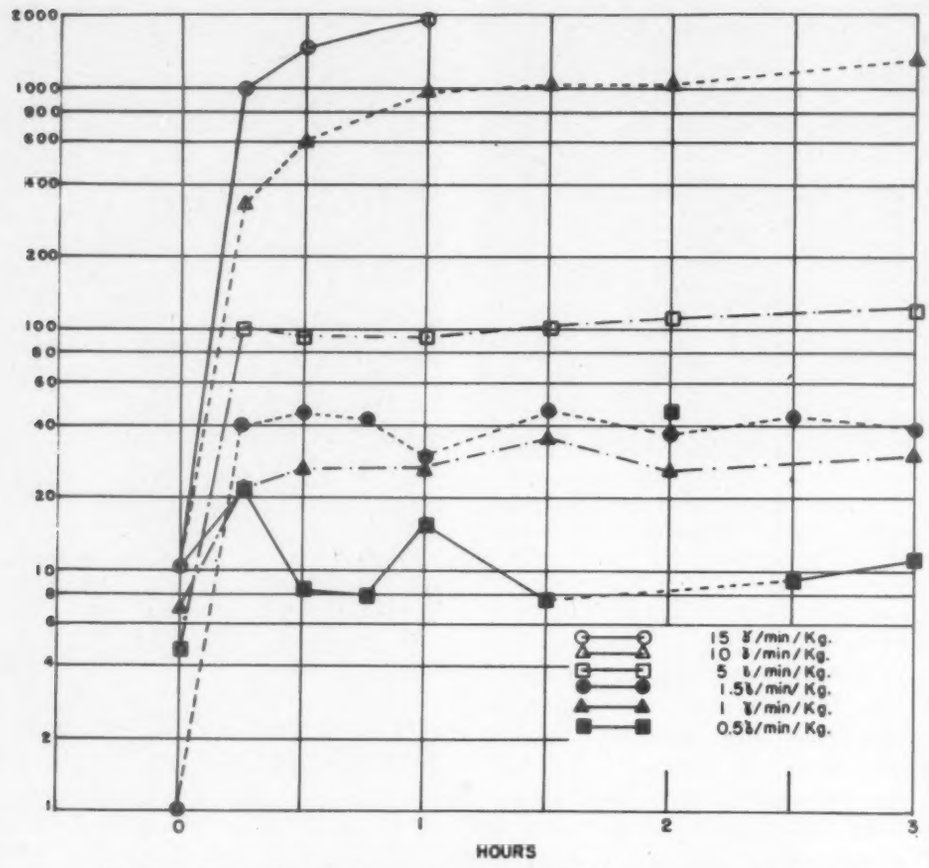

FIG. 9. Plasma levels of norepinephrine during constant rate infusion.

are treated with 1 μg. per minute per kg. of norepinephrine, medial necrosis of the aorta develops (Fig. 8). In untreated dogs in hemorrhagic shock or normal dogs infused with varying quantities of norepinephrine medial necrosis did not develop. Medial necrosis is common in rabbits but the dog is known to be resistant to aortic lesions.

Correlation of Dosage, Plasma Levels and Pathologic Changes: The first two diagrams (Figs. 3 and 4) contain information relative to the plasma catecholamine levels. In the individual animals in question there was no apparent correlation between pathologic changes and plasma norepinephrine content. Tissue-bound catecholamines are certainly more important than those contained in plasma in the pathogenesis of myocarditis. Absorption and accumulation of this substance in the myocardium and arteries has been reported.[17] Unfortunately, we did not determine tissue levels of catecholamines in our experimental material.

The data obtained from blood catecholamine determinations are plotted on a semilogarithmic scale against time representing the duration of the constant rate infusions (Fig. 9). The plasma norepinephrine rapidly increases in the first fifteen minutes and then levels off with dosages between 1 to 5 μg. per minute per kg. With higher doses the original rapid increase continues, reaching 2,000 μg. per L. It is interesting to note that 0.5 μg. per minute per kg. produces no sustained high plasma levels. Apparently the physiologic mechanism is competent to clear the infused norepinephrine in that amount. Upon termination of the infusion of norepinephrine the plasma levels return rapidly to normal when moderate doses are employed. With higher doses the disappearance curve shows an early rapid component and a later very slow one. Similar findings were recently presented by Axelrod[18] for epinephrine (Fig. 10).

Control levels of plasma norepinephrine in our experiments were elevated, averaging 6 μg. per L. Two factors were responsible for this, morphine premedication[19] and strapping of the dogs to the table. Both factors are known to increase the plasma catecholamine levels. Table 1 summarizes arterial plasma epinephrine

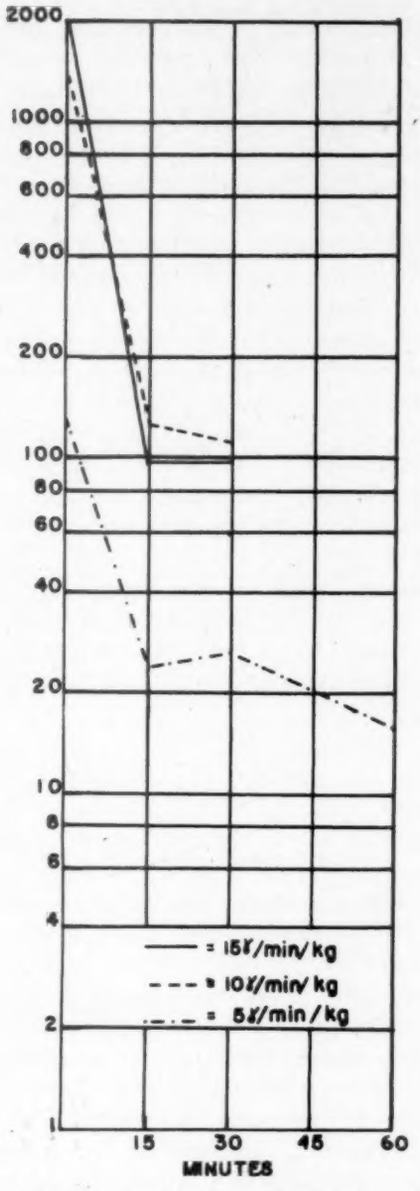

FIG. 10. Plasma levels of norepinephrine after the infusion terminated.

and norepinephrine levels under constant rate infusions for up to ten hours. The data refer to single animals. Three animals received the same dosage in the three low level infusion groups (0.5 μg., 1 μg. and 1.5 μg.), and the one with norepinephrine levels closest to the medium values was entered in the table. The variation amounted to less than 10 μg. per L. of norepinephrine.

The actual number of experimental animals and the correlation between dosages, arrhythmia and pathologic changes are shown in Table II. Arrhythmia and pathologic changes developed in approximately two-thirds of the

TABLE I

Arterial Plasma Catecholamine Levels During Constant Rate Infusions*

Norepinephrine Infusion	0.5 μg.	1 μg.	1.5 μg.	5 μg.	10 μg.	15 μg.
Plasma Norepinephrine Levels						
Control	1.7	7.8	0.2	4.8	10.6	10.6
15 min.	21.3	23.2	39.0	102.1	327.0	996.0
30 min.	8.2	26.3	49.9	93.1	607.0	1450.0
1 hr.	15.2	52.3	30.3	93.6	973.0	1910.0
3 hr.	11.0	29.9	39.1	124.6	1318.0	...
6 hr.	11.4	21.6	51.5	...	...	...
10 hr.	5.3	27.1	63.8	...	...	...
Plasma Epinephrine Levels						
Control	5.1	2.4	1.9	1.7	2.1	2.1
15 min.	3.6	3.7	0.9	2.6	7.2	14.9
30 min.	1.8	1.6	1.2	3.1	2.9	14.6
1 hr.	3.3	4.8	1.2	4.2	9.6	65.1
3 hr.	2.8	2.4	1.4	3.0	4.9	...
6 hr.	3.2	1.8	1.6	...	...	...
10 hr.	...	1.8	1.6	...	...	...

* Norepinephrine infusion is given per minute per kg.; plasma catecholamine levels in μg. per L.

TABLE II

Correlation Between Norepinephrine Dosage, Arrhythmias and Pathologic Changes in Twenty-Eight Experiments on Dogs

Dose Rate of Norepinephrine	Length of Treatment (hr.)	No. of Animals	Arrhythmia Developed	Pathologic Changes	
				Gross	Gross and Microscopic
Controls	24	2	...	...	...
0.5 μg./min./kg.	10	3	...	...	...
1 to 1.5 μg./kg./min.	< 6	3	1	1	1
	10	8	5	3	7
	>17	2	2	2	2
2 to 4 μg./kg./min.	< 6	3	2	2	3
5 μg.	6	3	3	3 (1 died)	3
10 μg.	3	3	3	3 (2 died)	3
15 μg.	1	1	1	1	1

animals in the 1 to 1.5 μg. per minute per kg. dose range. Further statistical treatment is not in order, but it should be emphasized that 0.5 μg. per minute per kg. produced no untoward effects, and a dose of 1 μg. per minute per kg. in the dogs treated appeared safe for up to six hours. Higher dosages or prolongation of the infusion would defeat the purpose of norepinephrine treatment, at least in the dog, by provoking tachycardia, drop in blood pressure,

cardiac arrhythmias of increasing severity, myocarditis and death.

Three of the animals died during the experimental period. In one, who received 5 μg. per minute per kg. of norepinephrine, pulmonary edema developed and it died after five hours of treatment. Of the two animals in the group which received 10 μg. per minute per kg., one died of cardiac arrest only thirty minutes after the treatment began, in the other massive cerebral hemorrhage developed and it died after two and a half hours of treatment. In the dog treated with 15 μg. per minute per kg. for one hour shock developed on termination of the infusion and it died two hours later.

Comments

Prolonged infusion of norepinephrine for therapeutic purposes has its limitations in man as it does in experimental animals. The myocarditis and vascular lesions found in patients following prolonged therapy with norepinephrine are not different from those produced in experimental animals. In the dog we were able to demonstrate that both pressor effects and bradycardia (the basis for therapeutic use) are transitory with doses above 1 μg. per minute per kg., and that a dose of 1 μg. is safe only up to six hours. Effective therapeutic doses for the dog should be kept below that level if prolonged treatment is anticipated. For short periods of time higher doses may prove effective and safe. Accumulation of toxic amounts of catecholamines in the tissues should not be allowed. Such accumulation in the cardiovascular system has been well demonstrated by Raab[17] and it is supported by the finding of a slow component in our curve of the disappearance of norepinephrine from the plasma (Fig. 10). One-half μg. per minute per kg. of norepinephrine in dogs produces no untoward effect and comparably small doses in man can be beneficial and well tolerated.

From the data presented it is apparent that the therapeutic dosage based only on estimations of blood pressure cannot be separated from toxic doses since the pressure response depends on vascular reactivity as well as on the circulating norepinephrine levels in blood. The physiologic response, at least the contractile force of the left ventricle,[20] was found to reach a maximum, even in acute experiments, with about 2 μg. per minute per kg. of norepinephrine in the vagotomized dog. Therefore, higher dosages even in short term treatments are not warranted. The pressure response to norepinephrine is higher in man than it is in the dog. If this observation can be applied on a purely empirical basis for man, the maximum safe dose should be one-fourth of the amount of 0.8 μg. per minute per kg. found for the dog if prolonged therapy with norepinephrine is planned. Poor response to therapy was observed in patients who received higher doses of norepinephrine. The pathologic changes now documented by autopsy in patients infused with pressor amines or suffering with pheochromocytoma, and produced in experimental animals even with "therapeutic" doses are convincing enough to necessitate setting an upper limit on a dose per kg. basis and not based on the blood pressure response alone. It is evident also that other means should be employed in the so-called "hopeless" cases and as a "last resort," since norepinephrine can offer only additional and severe injury in such circumstances.

Summary

The effects of constant rate intravenous infusions of norepinephrine were studied in twenty-eight normal dogs sedated with morphine. The range of dose rates in this experiment was from 0.5 to 15 μg. per minute per kg. Blood levels of epinephrine and norepinephrine were determined in twelve animals for up to ten hours during constant rate infusions.

The heart rate and blood pressure were recorded at frequent intervals. The reflex bradycardia was reversed in the animals by prolonged infusions of 1 or more μg. per minute per kg. of norepinephrine. In the animals in whom myocardial lesions developed, tachycardia and arrhythmia were regularly present. Death occurred due to cardiac arrest, massive cerebral hemorrhage or pulmonary edema in the animals infused with 10 μg. per minute per kg. for one-half to three hours, or 5 μg. per minute per kg. for six hours.

Postmortem examination was performed on all animals. The tissue changes were described and correlated with dosage rate and blood catecholamine levels.

The experimental results were discussed in the light of the mounting frequency of myocarditis due to pressor amine therapy in human beings and preventive measures in the form of a maximum safe dosage were offered.

Acknowledgment

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Some Similar Effects After Large Doses of Catecholamines and Myocardial Infarction in Dogs*

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STUDIES in this laboratory have revealed several similarities in dogs between the effects of administration of large doses of catecholamines, and myocardial infarction. Both coronary occlusion and the intravenous infusion of a large amount of norepinephrine or epinephrine produce a long lasting state of ventricular hypersensitivity,[1,2] during which small doses of catecholamines induce ventricular tachycardias. The ventricular hypersensitivity is associated with myocardial fatty changes, which are widespread after administration of the amine,[1] but restricted largely to the area around the infarct after coronary occlusion.[3,4] Serum transaminases and lactic dehydrogenases are known to be elevated after myocardial infarction, and we have reported elevations of serum transaminases after administration of large doses of norepinephrine and epinephrine.[5]

The present report is a comparison of the ventricular sensitivity, the triglyceride content of the heart and serum enzyme levels after myocardial infarction and after administration of large doses of catecholamines in the dog. Administration of the adrenergic blocking agent, phenoxybenzamine, prevented almost all the changes after infusion of large doses of the catecholamines, but did not modify the effects of myocardial infarction.

METHODS

The studies were carried out on mongrel dogs of both sexes weighing 7 to 17 kg.

Surgical Procedures: Surgery was performed aseptically in dogs anesthetized with sodium pentobarbital. Myocardial infarction was produced by ligation of the anterior descending coronary artery by the two-stage occlusion procedure of Harris[6] at the level of the tip of the left atrium. The infarcts were large, about 4 to 5 cm. in diameter, as previously described.[3] In sham operations, the heart was exposed for at least thirty minutes as in the ligation procedure.

Drugs: Doses of the catecholamine group are expressed in terms of the free bases. A commercial solution of the bitartrate of l-norepinephrine (Levophed®) was diluted with isotonic saline shortly before use. Large doses of norepinephrine were administered intravenously in unanesthetized dogs by continuous infusion, using a Bowman pump. Dogs received either 0.51 or 0.85 mg. per kg. norepinephrine in 20 to 90 ml. of saline. The rates of infusion varied from 3.3 to 9.7 μg. per kg. per minute. A suspension of epinephrine in peanut oil (Adrenalin® in oil), 1 mg. per kg., was injected subcutaneously.

Phenoxybenzamine (dibenzyline) hydrochloride (1 mg. per ml.) was dissolved in saline and injected intravenously in a dose of 2 mg. per kg. one hour before infusion of a large dose (0.85 mg. per kg.) of norepinephrine.

Test Doses: Many of the dogs received a test dose of norepinephrine (9.5 μg. per kg.) before and at varying times after coronary ligation or after an infusion of a large amount of a catecholamine. Maximum ectopic rates induced by the test doses were determined from lead II electrocardiograms, as described in a previous report.[2] Ventricular tachycardias induced by test doses indicated myocardial hypersensitivity.

Measurement of Serum Enzyme Levels: Serum glutamic oxalacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) were measured by the method of Reitman and Frankel.[7] Serum alkaline phosphatase (SAP) was measured by the method of Bodansky; the phosphate liberated was determined by the method of Fiske and Subbarow. Serum lactic dehydrogenase (SLD) was determined by the procedure of Cabaud and Wroblewski.[8]

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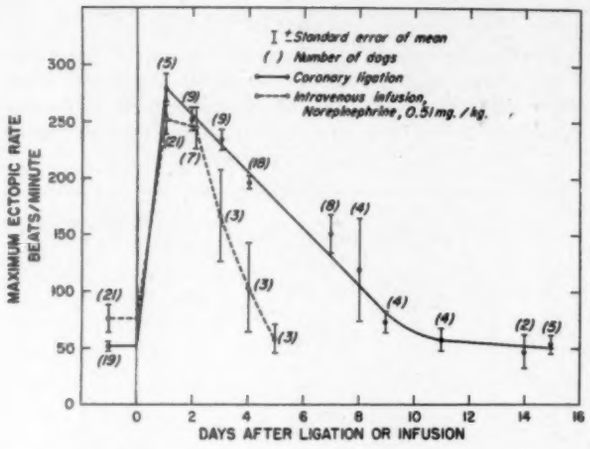

FIG. 1. Prolonged ventricular hypersensitivity after an intravenous infusion of norepinephrine, 0.51 mg. per kg., compared with the hypersensitivity after coronary ligation. The points represent the mean maximum ectopic rates during the responses to test doses of norepinephrine, 9.5 μg. per kg. The curve representing the hypersensitivity after an infusion of norepinephrine is taken from a previous paper.[1] The curve representing the hypersensitivity after coronary ligation is taken from a paper published in 1957.[2]

Measurement of Heart Triglyceride: The heart muscle was carefully trimmed to remove the coronary arteries and the epicardium, which contains many fat cells. The triglyceride content of heart muscle was measured by a modification of the direct colorimetric method of van Handel and Zilversmit.[9]

RESULTS

Ventricular Hypersensitivity: Both coronary ligation[2] and intravenous infusions of large doses of norepinephrine or epinephrine[1] produced a sustained ventricular hypersensitivity (Fig. 1). The maximum ectopic rates induced by test doses of norepinephrine were about the same on the first day after either occlusion or infusion. The hypersensitivity after coronary occlusion persisted longer; the responses did not become normal until about four days after infusion and ten to twelve days after occlusion.

Myocardial Fatty Changes and Triglyceride Deposition: During the period of marked hypersensitivity after an infusion of a large dose of a catecholamine, frozen sections stained for neutral fat with oil red O revealed numerous fine lipid droplets in myocardial fibers.[1] This suggested triglyceride deposition. Measurement of the triglyceride content of the heart showed a two- to fourfold increase in the dogs which died within twenty hours or were sacrificed the day after infusion of a large dose (0.85 mg. per kg.) of norepinephrine (Table 1). The intravenous injection of 2 mg. per kg. of the adrenergic blocking agent phenoxybenzamine, one hour before the infusion, prevented the triglyceride deposition.

TABLE 1

Triglyceride Deposition in the Dog's Heart Induced by an Infusion of Norepinephrine, 0.85 mg. per kg., and Its Prevention by the Adrenergic Blocking Agent, Phenoxybenzamine

Treatment	Heart Triglyceride (gm./100 gm. heart)	No. of Hearts	Standard Error of Mean
Controls	0.27	14	±0.03
Norepinephrine infusion, 0.85 mg. per kg. intravenously in 135 to 168 minutes*	0.71	5	±0.16
Norepinephrine infusion, 0.85 mg. per kg. intravenously in 146 to 165 minutes, 1 hour after 2 mg. per kg. of phenoxybenzamine	0.26	4	±0.04

* Two dogs died within eight to twenty hours after infusion. There were no deaths among the four dogs pretreated with phenoxybenzamine. Survivors were sacrificed twenty-two to twenty-six hours after infusion.

The fatty changes around myocardial infarcts gradually disappeared in about fourteen days,[3] confirming the results of Wartman and coworkers.[4] The triglyceride content of the myocardium bordering the infarcted areas was greater than that of uninfarcted myocardium, as shown in unpublished experiments.[10] Thus, triglyceride deposition in the myocardium is associated with the hypersensitivity after both coronary occlusion and infusions of large doses of catecholamines.

Serum Enzyme Levels: We have previously reported[5] marked elevations in SGOT, SGPT and SAP after large doses of epinephrine and norepinephrine. Raab[11] has also observed marked increases in serum transaminase after injections of large doses of epinephrine. Other investigators[12–15] have reported elevations in SGOT, SGPT and SLD after experimental myocardial infarction in dogs. We have confirmed the elevations in SGOT, SGPT and SLD after coronary occlusion; we find that SAP is also increased. In our experiments, the changes after sham operations were minor compared to the marked

TABLE II

Mean Increase, ± Standard Error of the Mean, in Serum Enzyme Levels Within Eighteen to Twenty-Four Hours After Coronary Artery Ligation or Sham Surgery

Enzyme	Coronary Ligation (19 dogs)	Sham Operation (2 dogs)
SGOT	649.4 ± 87.4	66.0 ± 39.0
SGPT	241.5 ± 30.9	9.5 ± 2.5
SLD	628.2 ± 122.2	−97.5 ± 147.5
SAP	6.9 ± 1.7	1.7 ± 0.6

serum enzyme elevations after coronary artery ligation (Table II).

The elevations in SGOT after our infusions of norepinephrine were less marked than those after occlusion (Fig. 2). The SGOT levels were normal by the third day after either an infusion or coronary ligation. After infusions significant elevations occurred in the four serum enzymes measured, with peak values in about five to six hours (Fig. 3). SGOT increased relatively more than the other enzymes.

Intravenous injection of 2 mg. per kg. of the adrenergic blocking agent, phenoxybenzamine, one hour before infusion prevented the elevations in SGOT, SGPT and SLD (Table III). Phenoxybenzamine did not prevent the increase in SAP. It also did not prevent the elevations in

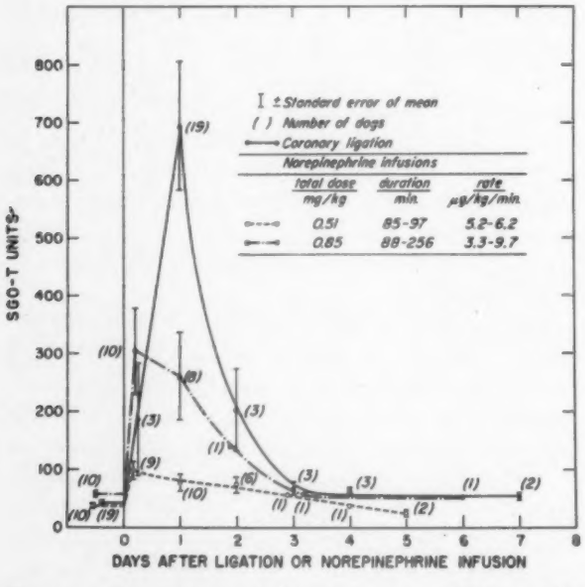

FIG. 2. Comparison of the changes in SGOT which occurred in unanesthetized dogs after intravenous infusions of norepinephrine (dashed lines) with the greater increases measured in nineteen dogs after ligation of the anterior descending coronary artery (solid line).

TABLE III

Mean Increase in Serum Enzyme Levels, ± Standard Error of the Mean, Within Five to Six Hours After the Beginning of an Infusion of Norepinephrine in Dogs Without Prior Treatment and in Dogs Pretreated with Phenoxybenzamine

Enzyme	Norepinephrine Infusion* 0.85 mg. per kg. (values measured in 6 to 10 dogs)	Norepinephrine Infusion, 0.85 mg. per kg., 1 hour after Phenoxybenzamine, 2 mg. per kg. (4 dogs)
SGOT	248.7 ± 76.2	16.0 ± 12.3
SGPT	103.5 ± 51.2	1.5 ± 2.5
SLD	345.0 ± 193.3	−66.2 + 111.2
SAP	1.8 ± 0.5	1.9 ± 0.8

* The rates of infusion varied from 3.3 to 9.7 µg. per kg. per minute.

serum enzymes after myocardial infarction.[16]

Elevations in serum enzymes as great as those after coronary occlusion occurred after subcutaneous injection of epinephrine in oil,[5] 1 mg. per kg. (Figs. 4 through 7). Comparable ele-

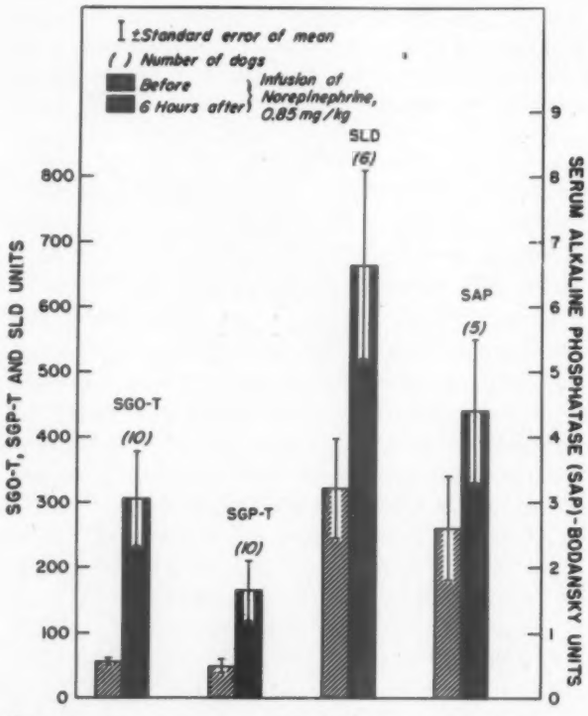

FIG. 3. Serum enzyme levels before and six hours after the infusion of norepinephrine, 0.85 mg. per kg. The rates of infusion varied from 3.3 to 9.7 µg. per kg. per minute. Each vertical bar represents the mean serum enzyme level measured in the number of dogs indicated in the parentheses. The enzymes measured were SGOT, SGPT, SLD and SAP.

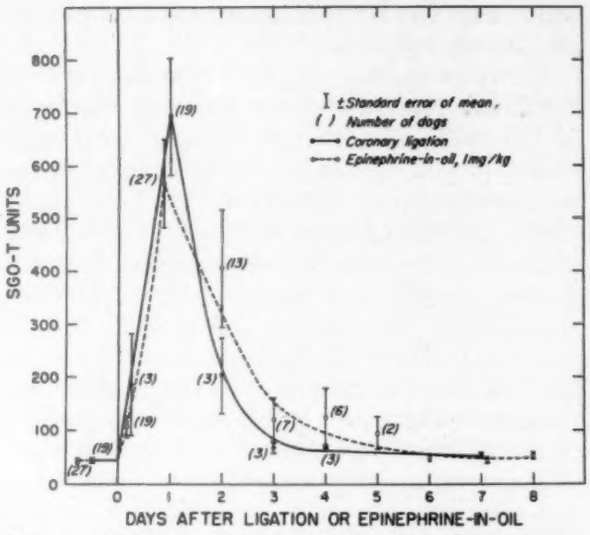

FIG. 4. SGOT levels in dogs before and after coronary ligation (solid line) or administration of epinephrine in oil, 1 mg. per kg. subcutaneously (dashed line).

vations in serum enzymes also occurred in a dog after intravenous infusion of 1 mg. per kg. epinephrine in five and a half hours.[5] Epinephrine in oil was absorbed too slowly to cause a significant rise in arterial blood pressure in two dogs in which femoral arterial pressure was recorded with a Statham P23D transducer for six hours after the subcutaneous injection.[5] The infusions of norepinephrine and epinephrine produced substantial rises in blood pressure, as previously described.[1]

The elevations in SGPT after coronary occlusion are greater in the dog[15] (Fig. 5) than in man. Ruegsegger and co-workers[15] have shown that the heart of the dog contains an appreciable amount of this enzyme and that the human heart contains relatively little.

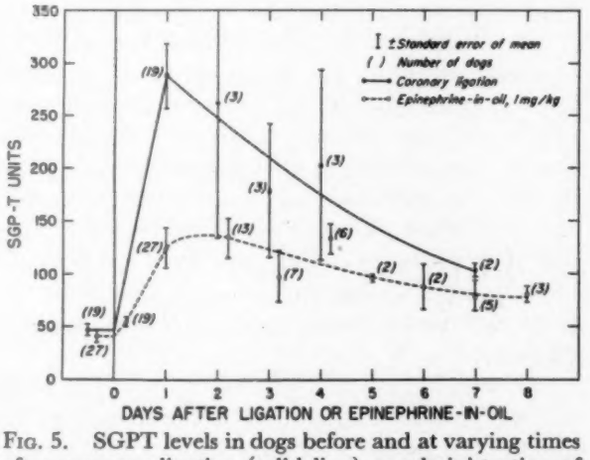

FIG. 5. SGPT levels in dogs before and at varying times after coronary ligation (solid line) or administration of epinephrine in oil, 1 mg. per kg. subcutaneously (dashed line).

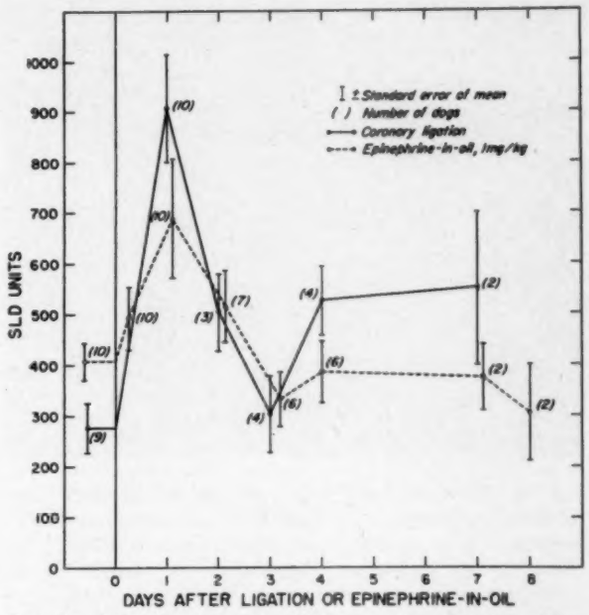

FIG. 6. SLD levels in dogs before and at varying times after coronary ligation (solid line) or administration of epinephrine in oil, 1 mg. per kg. subcutaneously (dashed line).

The peak elevations in SLD after administration of epinephrine in oil were slightly, but not significantly, less than after coronary ligation (Fig. 6). SLD values fluctuated considerably

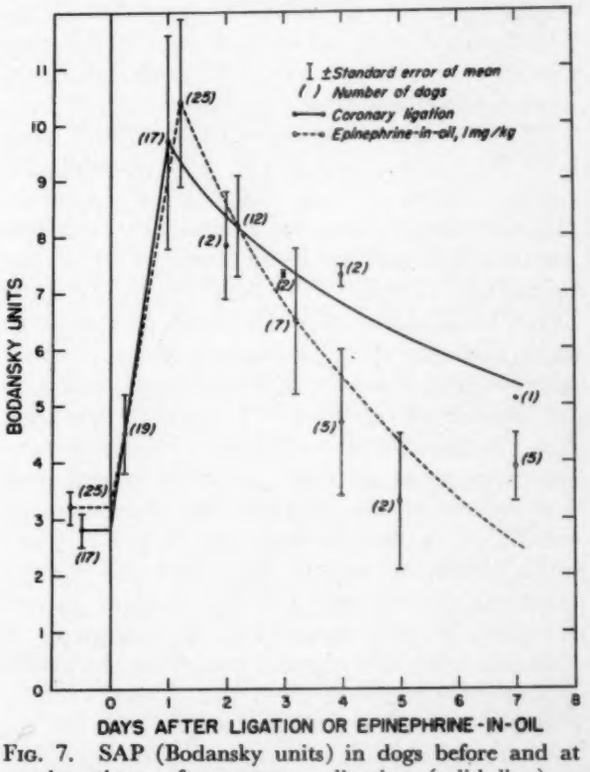

FIG. 7. SAP (Bodansky units) in dogs before and at varying times after coronary ligation (solid line) or administration of epinephrine in oil, 1 mg. per kg. subcutaneously (dashed line).

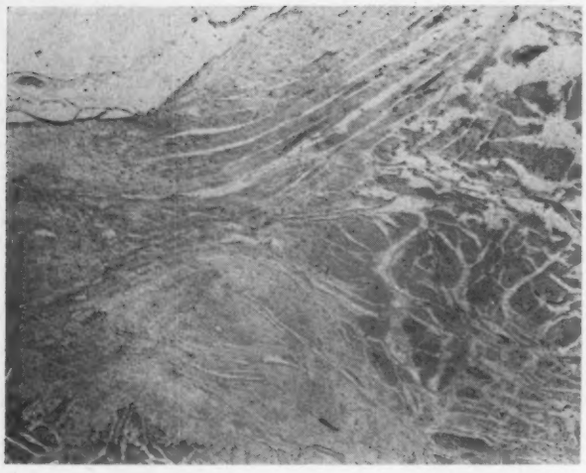

FIG. 8. Section of the heart, stained for alkaline phosphatase by Gomori's method, from a dog sacrificed fourteen days after ligation of the anterior descending coronary artery. Alkaline phosphatase is stained black. *Above*, normal myocardium. *Below*, infarcted myocardium. Note almost complete absence of alkaline phosphatase in the endothelium of capillaries in the infarcted area. Original magnification × 25.

three to eight days after either injection of epinephrine in oil or coronary ligation. The transaminases are probably a better index of myocardial damage in the dog than SLD because the relative increase in SGOT is greater and the transaminase levels in control dogs and during recovery from experimental procedures are more reproducible from day to day.

Serum alkaline phosphatase was elevated after both coronary ligation and administration of epinephrine in oil (Fig. 7). Part of the elevation after ligation was the result of thoracic surgery, as indicated by the small rise after a sham operation (Table II). Sections of normal heart, infarcted heart and heart from dogs sacrificed one day after infusion of large doses of norepinephrine were stained by Gomori's method for alkaline phosphatase. No appreciable alkaline phosphatase was detected within the myocardial fibers in any dog. Alkaline phosphatase was present in the endothelium of myocardial capillaries in control dogs and dogs sacrificed after administration of large doses of norepinephrine, but was almost absent in the endothelium of infarcted areas (Fig. 8). However, it does not seem likely that the amount of alkaline phosphatase released from the capillary endothelium would be sufficient to account for the pronounced rise after coronary occlusion; in our experiments, the rise was comparable to that found after massive infarction of the kidney,[17] which contains a much higher concentration of alkaline phosphatase.

Damage to the liver may also contribute to the elevations of all the serum enzymes, especially SGPT and SAP, after administration of catecholamines or coronary ligation. Large doses of catecholamines sometimes produced fatty changes in other organs, especially the liver and kidney.[5] However, the fatty changes in other organs after infusions of large doses of catecholamines were less constant and marked than in the heart. These histologic findings may be related to "the specific avidity of the heart muscle to absorb and store epinephrine and norepinephrine," which was first reported by Raab and Gigee,[18] and recently confirmed by Axelrod and co-workers.[19]

COMMENTS

We were surprised that the serum enzyme elevations were greater after administration of epinephrine in oil than after our infusions since the histologic changes were less constant and severe. Significant ventricular hypersensitivity did not occur after administration of epinephrine in oil, but was marked after our infusions. The fatty changes in the heart and other organs after administration of catecholamines indicate that part of the elevations in serum enzymes is the result of cellular damage.[1,5] However, part of the rise in serum enzymes after infusion of catecholamines may be the result of an accelerated synthesis or decreased utilization and elimination of the enzymes. Hauss and Leppelmann[20] discuss the factors influencing enzyme levels in serum; they do not think that cellular damage alone is sufficient to explain the changes in serum enzyme levels which they have measured in human patients and in animals.

The usefulness of SGOT, SGPT and SLD determinations in the diagnosis of myocardial infarction may be subject to limits since the elevations in these serum enzymes after administration of epinephrine in oil were as great as after ligation of the anterior descending coronary artery (Figs. 4 through 6). Our findings suggest that release of epinephrine from the adrenal medulla after various stresses may contribute to some elevations in serum enzyme levels observed clinically.

Administration of the adrenergic blocking agent, phenoxybenzamine, prevented the triglyceride deposition (Table I), the elevations in SGOT, SGPT and SLD (Table III) and the ventricular hypersensitivity after infusions of large

doses of catecholamines. It also prevented the elevations in SGOT and SGPT after administration of epinephrine in oil. Administration of phenoxybenzamine did not prevent the triglyceride deposition, the ventricular hypersensitivity and the serum enzyme elevations after coronary occlusion.[16] Depletion of the norepinephrine content of the heart by administration of reserpine also did not prevent these changes after occlusion.[16]

Summary

In dogs, both myocardial infarction and administration of large doses of catecholamines produce sustained ventricular hypersensitivity, as indicated by exaggerated ectopic responses to administration of small doses of norepinephrine. This hypersensitivity is associated with myocardial fatty changes. The triglyceride content of the heart is elevated the day after an infusion of a large amount of norepinephrine. Both myocardial infarction and administration of large doses of catecholamines cause marked elevations in serum glutamic oxalacetic and glutamic pyruvic transaminases, lactic dehydrogenase and alkaline phosphatase. The adrenergic blocking agent, phenoxybenzamine, prevents the triglyceride deposition in the heart, the prolonged ventricular hypersensitivity and the elevations in serum transaminases and lactic dehydrogenase after large doses of catecholamines; it does not prevent these changes, however, after coronary occlusion.

Acknowledgment

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Amine Oxidase Inhibitors in the Treatment of Angina Pectoris

Preliminary Report on Marplan and Tersavid*

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CESARMAN[1] in Mexico and later Cossio[2] in Argentina observed that iproniazid (Marsilid®) appeared to relieve the pain of angina pectoris. These observations, which have now been confirmed by others,[3–10] stimulated two types of investigations: (1) a systematic search for similar compounds of greater efficacy and safety; and (2) a pursuit of the mode of action in the amelioration of this disorder.

Of the many derivatives of iproniazid which have recently been presented for clinical trial, we have conducted the preliminary clinical studies on five, two of which appear to be promising in the management of angina pectoris. The chemical structures are shown in Figure 1.

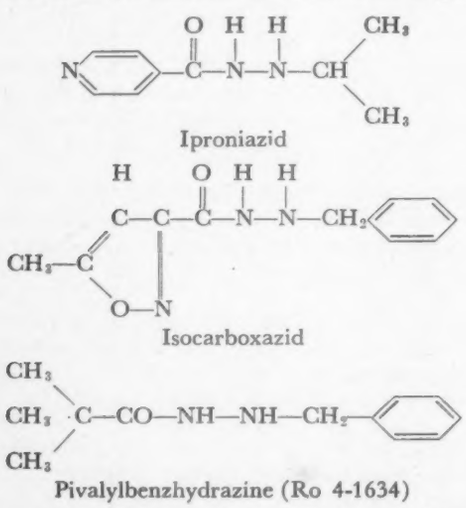

FIG. 1. Structural formulas of iproniazid (Marsilid) isocarboxazid (Marplan) and pivalylbenzhydrazine (tersavid).

Ro 5-0831/1 (isocarboxazid [Marplan,® Roche]) is 1-benzyl-2-(5-methyl-3-isoxazolylcarbonyl) hydrazine. Pharmacologic studies indicate that although this derivative is somewhat less toxic than the parent compound, it is considerably more potent as an amine oxidase inhibitor.[11,12] A more favorable therapeutic ratio is therefore suggested.

Between November 1, 1958 and March 30, 1959, isocarboxazid was administered to twenty-seven patients with angina pectoris. The group ranged in age from forty-six to eighty-six years (average sixty-one years) and consisted of fifteen men and twelve women. Treatment was carried out for one to sixteen weeks (average 7.7 weeks) with thirteen patients treated eight weeks or longer. The dose ranged from 5 to 30 mg. per day. The doses most commonly used were 10 and 20 mg. per day. In addition to the administration of the active drug, a period of placebo medication was introduced for thirteen patients. This period ranged from two to seven weeks (average 3.6 weeks).

The degree of angina pectoris was evaluated according to the severity of pain, the number of attacks of angina per week and the average number of nitroglycer n tablets used per day. Severity was graded from 1 to 4 as follows: (1) absent or barely noticeable pain; (2) definite pain, but no interference with daily routine; (3) pain which causes brief pauses in usual activity; and (4) almost completely disabling pain.

The patients were also questioned concerning

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TABLE I
Summary of Results in Treatment of Angina Pectoris

Result	Duration of Treatment	
	Less than 2 Weeks	Greater than 2 Weeks
A. Isocarboxazid		
Excellent	0	11
Good	1	5
Fair	0	4
Failure	3	3
Totals	4	23
B. Pivalylbenzhydrazine		
Excellent	2	21
Good	0	15
Fair	1	9
Failure	5	15
Totals	8	60

their capacity for effort, and specifically regarding the presence of side effects.

RESULTS

ISOCAREOXAZID (MARPLAN)

The response was considered to be excellent when angina pectoris was completely eliminated or was so reduced in severity and frequency that it no longer represented a problem to the patient. The result was considered a failure when the condition was not improved or became worse. The terms "fair" and "good" were applied when the response was favorable but incomplete.

The results are tabulated in Table 1A. In twenty-three subjects the periods of treatment were longer than two weeks. Of these, the results were considered excellent in eleven, good in five and fair in four; there were three failures. Of the four patients treated for two weeks or less the results were good in one and failures in three. This included three patients who stopped treatment of their own accord in this short period of time. The prior experience of many of these patients with the long-acting nitrites and other commonly used medications had been poor; therefore, these results were considered to be encouraging.

Comparison with Placebo Medication: As noted, a period of placebo medication was carried out in thirteen patients. Of these, seven had had a good or excellent result when given the active drug and suffered an exacerbation of symptoms during the placebo period. Three patients had a good result while receiving isocarboxazid and the benefit was maintained during the placebo period. Two patients who received the placebo as the initial medication and benefited therefrom maintained their benefit when the active drug was substituted. One patient did not improve on either the placebo or the active medication. One patient, noted in the first group, suffered a late exacerbation while receiving isocarboxazid.

Laboratory Studies: The following laboratory studies were made at weekly intervals: complete blood count, urinalysis, blood urea nitrogen, alkaline phosphatase and SGOT determinations. Cephalin flocculation, serum bilirubin and reticulocyte count determinations were carried out occasionally. There were no significant changes in these values during the study period. Small amounts of albumin were noted in the urine of seven patients and larger amounts in two. This is not a remarkable finding for this type of patient or specifically for these patients.

Side Effects: Clinical side effects were reported by thirteen patients. In three, orthostatic hypotension with syncope was noted. Other complaints mentioned were weakness (four), dizziness (three), insomnia (two) and euphoria, fatigue, palpitations, constipation, dry mouth and tremor (one each).

During the course of the study two elderly arteriosclerotic patients, aged seventy-five and eighty-six years, and one fifty-seven year old man known to have a severe degree of coronary artery disease died of myocardial infarction. These events are not unusual in such patients with angina pectoris and are probably not related to use of the drug. Two patients, aged sixty-seven and seventy-two, had cerebrovascular accidents. That orthostatic hypotension could have been a contributing factor is a possibility. One subject, who had normal blood pressure at the time, collapsed after venipuncture.

PIVALYLBENZHYDRAZINE (TERSAVID)

More recently, Ro 4-1634 (pivalylbenzhydrazine [tersavid, Roche]), which chemically is 1-benzyl-2-trimethylacetyl-hydrazine, became available. Pharmacologic studies indicate that

this compound is less toxic than iproniazid and two to three times as potent as a monoamine oxidase inhibitor.[12] As of this date seventy-eight patients with angina pectoris have been treated, sixty-eight of whom are available for evaluation. This latter group consists of forty-two men and twenty-six women ranging in age from thirty-six to eighty-two years (average fifty-nine years). The medication was given for two weeks to eleven months (average three months) in dose range of 50 to 150 mg. per day (average 75 mg. per day). The methods of study, evaluation and laboratory controls were exactly as described for isocarboxazid in all details.

Results and Side Effects: Our preliminary evaluation is summarized in Table 1B. In the sixty patients who received the medication for longer than two weeks, the results were good to excellent in thirty-six, fair in nine and failures in fifteen. Perhaps more important, however, was the conspicuous lack of significant side effects, and the absence of adverse changes in the laboratory values. Eleven patients of the total group of seventy-eight reported one or two of the following: dizziness, stomach cramps, palpitations, insomnia, sensation of warmth, throbbing of the head, gaseous eructation, depression and euphoria. These are, of course, common complaints in elderly arteriosclerotic patients. Thus, sixty-seven patients reported no side effects whatever, and in no case was it necessary to discontinue the medication. However, during the period of study three subjects suffered myocardial infarctions and eight others experienced prolonged bouts of pain in the chest considered to represent episodes of coronary insufficiency.

These early clinical observations suggest that pivalylbenzhydrazine is an exceptionally safe amine oxidase inhibitor which may be useful in the symptomatic treatment of angina pectoris. It does not appear to alter the basic disease process. Double-blind studies have been initiated in these and other patient groups to further delineate its value.

Comments

The results of the use of isocarboxazid in angina pectoris reported here are, in general, consistent with the experiences of others.[13–16] Russek noted a lower incidence of improvement with Ro 4-1634, but was also impressed with the lack of side effects.[15] The difficulties in evaluating agents for the treatment of such a subjective and variable disorder as angina pectoris are well appreciated. However, two observations seem warranted at this time. First, some, but not all, derivatives of iproniazid possess antianginal properties. This leads to the hope that the intensive efforts now in progress to define the chemical and pharmacologic characteristics associated with antianginal activity will lead not only to more effective therapeutic agents, but perhaps also to further understanding of the pathologic physiology of the anginal syndrome. Second, the clinical effects in some patients are such that we believe the monoamine oxidase inhibitors represent a significant advance in the management of patients with angina pectoris.

Amine Oxidase Inhibition, Catecholamines and Angina Pectoris: A consideration of possible mechanisms of action of the amine oxidase inhibitors in relieving anginal pain must begin with the enzyme that is inhibited, amine oxidase, and with the principal physiologic substrates, epinephrine, norepinephrine and serotonin. All three qualify as coronary dilators.[17–22] However, significant reservations are quickly encountered. The catecholamines appear to carry certain liabilities, particularly increased myocardial oxygen consumption, increased mean arterial blood pressure, and adverse chronotropic effects.[18,23,24] Furthermore, Pletscher[22] has demonstrated that the pattern of action of norepinephrine on the hearts of rabbits and cats differs considerably from that associated with the perfusion of iproniazid. In addition, the extensive studies of Raab[25,26] would seem to suggest that the effects of the catecholamines in atherosclerotic heart disease are largely detrimental. Finally, there is evidence that the administration of iproniazid is not associated with changes in circulating catecholamines,[27–30] although in some species tissue levels are increased.

The amine oxidase inhibitor-catecholamine-cardiovascular relationships may, however, be considered from a negative point of view. Pletscher and Pellmont[22] have suggested these drugs may act by blocking the release of these biogenic amines. It has been shown that the intracellular accumulation of these hormones resulting from administration of an amine oxidase inhibitor decreases the sensitivity of vascular tissues to circulating norepinephrine.[31,32] Since the administration of iproniazid is associated with increased endogenous norepinephrine in the heart of several animal species,[33] a resultant

decreased sensitivity to exogenous catecholamines might exert a salutary effect in angina pectoris, if this could be shown to occur in man.[34]

Amine Oxidase Inhibitors and Serotonin: The identification of serotonin as the possible compound in the metabolic chain of events leading to relief of angina also carries objections, but they seem less imposing. In favor of such a hypothesis is the fact that the increased coronary blood flow following the infusion of serotonin is associated with decreased left ventricular work as a result of decreased peripheral resistance.[20] Although Granowitz and Pletscher[35] reported that the urinary excretion of 5-hydroxy-indolacetic acid, the end product of serotonin metabolism, was not affected by administration of iproniazid, Pletscher and Bernstein[36] later demonstrated an increase in platelet serotonin in response to administration of this drug and suggested that this might explain some of the effects on the heart. The ability of amine oxidase inhibitors to increase the serotonin content of peripheral tissues has also been noted by Shore.[37] In this respect Sjoerdsma,[38] working with several amine oxidase inhibitors in man, has demonstrated a marked decrease of the percentage conversion to 5-hydroxy-indolacetic acid of orally administered serotonin. These findings are consistent with the greater dependence of serotonin (versus the catecholamines) on amine oxidase for its degradation.

Direct Coronary Dilatation: Although dilatation of the coronary arteries can be accomplished experimentally by the direct infusion of iproniazid,[22,39] this effect is acute and transient, therefore unlike the delayed, prolonged effects observed clinically. Thus, this direct action is probably not responsible for the clinical effects in angina pectoris.

Oxygen Sparing Effects: These compounds interfere with a number of oxidative processes in addition to the oxidative deamination of serotonin and the catecholamines. It is possible, therefore, that such action might reduce the deleterious effects of anoxia on the myocardium.[34,40] Support for such a hypothesis is provided by the observations that pretreatment with iproniazid seems to offer some protection in dogs against the effects of acute coronary occlusion[41] and, in rats, against acute isopropylarterenol-induced myocardial necrosis.[40] The most cogent objections to this idea are that in the majority of the cases reported in the literature, as well as in our patients, no improvement in the electrocardiogram has been observed during treatment with these drugs, and the natural history of arteriosclerotic heart disease does not appear to have been altered.

Interference with Transmission of Pain: These observations lead to a discussion of still another possible mechanism: namely, that the relief of pain may be due to a central,[7,8,42] ganglionic[4] or peripheral[43] interference with transmission of pain. The well known psychostimulant properties of these drugs coupled with the recognized influence of emotional factors in the anginal syndrome, make the action on the central nervous system particularly suspect. The only argument of weight against this as the total explanation is the fact that Ro 4-1634 has little or no central nervous system activity, yet has considerable effect in relief of angina pectoris. Interference with transmission of pain at the ganglion level seems less likely since true ganglionic blockade cannot be confirmed experimentally in intact animals.[40,44] The possibility of peripheral analgesia is suggested by the studies of Emele and associates[45] and is currently under investigation by Randall and co-workers.[43]

Excellent reviews by Zbinden, Randall and Moe[40] and by Pletscher, Gey and Pellmont[34] discuss these and other considerations in greater detail. From the clinical point of view these drugs appear to be potent and reliable agents for the symptomatic relief of angina pectoris. However, until it is demonstrated that the amine oxidase inhibitors exert some salutary effect on a hemodynamic or metabolic process of the heart, patients so treated and responding favorably must be cautioned not to exceed appropriate physical activity.

Summary and Conclusions

Isocarboxazid (Marplan) was administered to twenty-seven patients with angina pectoris. Of the twenty-three patients who received the medication for two weeks or longer, the relief of pain was considered to be excellent in eleven, good in five, fair in four and failures in three. Clinical side effects were reported by thirteen patients. Except for orthostatic hypotension with syncope, these were minor and did not necessitate interruption of treatment. There were no significant abnormalities in the laboratory findings.

Pivalylbenzhydrazine (tersavid) was administered to seventy-eight patients with this disorder. Of these, sixty-eight are available for evaluation. Sixty patients received the medica-

tion for two weeks or longer. The relief of the pain of angina pectoris was considered to be excellent in twenty-one, good in fifteen and fair in nine; there were fifteen failures. No significant side effects were observed on either clinical or laboratory examination.

Current considerations of possible mechanisms of action of amine oxidase inhibitors in relieving anginal pain are briefly reviewed.

These preliminary clinical studies warrant the following observations: (1) some derivatives of iproniazid also possess antianginal properties; (2) there is no evidence at this time that the amine oxidase inhibitors interfere with the natural course of arteriosclerotic heart disease; and (3) the clinical effects in some patients are so marked that we believe these compounds represent a significant advance in the management of patients with angina pectoris.

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The Influence of Antihypertensive and Hypertensive Substances on Vascular Reactivity to Catecholamines*

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DURING the past fifteen years considerable insight has been gained concerning the neurohumoral mechanisms through which the central and peripheral actions of the sympathetic nervous system are mediated. As early as 1921 Loewi[1] had demonstrated the liberation of a cardioaccelerator substance when the vagus nerve of the frog was stimulated. Since the vagus trunk in this species contained both sympathetic and parasympathetic nerves, either speeding or slowing was seen, depending upon which type of fiber predominated. Loewi's studies on the cardiac slowing "vagus substance," which was ultimately identified as acetylcholine, is probably more famous but certainly of no greater significance than his contemporary observation of the liberation of a cardioaccelerator substance similar to epinephrine following sympathetic nervous stimulation.

In 1910, Barger and Dale[2] had noted a close resemblance between the effects of sympathetic nerve stimulation and the injection of epinephrine and other so-called sympathomimetic amines. In 1933, Cannon[3] named the sympathetic neuromediator substance "sympathin" upon observing certain differences between the effects of direct nervous stimulation and those of administration of epinephrine. The most striking divergence was found in the influence of ergotoxine upon their pressor effects, reversing that of epinephrine to depressor but only slightly reducing the effect of sympathin. As early as 1943 Raab[4,5] demonstrated the presence of catecholamines in the brains of rats. It was not until 1946 that von Euler[6] provided conclusive evidence of the presence of norepinephrine in extracts of sympathetic nerves and of organs which they innervated, thus affording objective support of its postulated role as the adrenergic nervous mediator. Significantly, the pressor effect of norepinephrine, like that of "sympathin," is not reversed by ergotoxine. Subsequently, evidence has been obtained by von Euler[7] that very small amounts of epinephrine are also formed by sympathetic nerves. The *in vivo* neurohormone seems, therefore, to be a mixture of norepinephrine and epinephrine, with the latter present at a small but significant level. If such is the case, norepinephrine would be equivalent to sympathin E and epinephrine would correspond to sympathin I in the nomenclature adopted in Cannon's sympathin theory of the mechanism of sympathetic nervous mediation. Von Euler has also shown the presence of norepinephrine in brain and demonstrated its relatively high concentration in the region of the sympathetic nervous centers in the hypothalamus. The adrenal medulla, which had long been known to be rich in epinephrine, has also been shown to contain a smaller but discrete quantity of norepinephrine.

Such recent advances in the knowledge of the underlying pharmacologic mechanisms involved in the normal function of the sympathetic nervous system have been a stimulus to the quest for agents capable of altering the reactivity of the cardiovascular system to neurohumoral sympathetic control. This search has been spurred by practical as well as theoretical considerations. It is known that the peripheral resistance is augmented by the vasoconstriction resulting from either stimulation of a sympathetic nerve or administration of norepinephrine. It is also known that in essential hypertension the peripheral resistance is increased.

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Although it has never been demonstrated that the increased resistance or elevated blood pressure of essential hypertension is due primarily to increased sympathetic neurohumoral activity, it has been shown by Smithwick[8] that surgical interruption of a sufficient number of sympathetic pathways by bilateral excision of the thoracolumbar ganglionic chains can lower the blood pressure in essential hypertension by decreasing the peripheral resistance. This achievement provided the impetus for the development of a number of substances which were designed with a view toward providing a so-called pharmacologic sympathectomy. It is of considerable interest that Raab and Maes[9] observed a decrease in the catecholamine content of heart muscle following sympathectomy.

Peripherally there are two regions at which the sympathetic nervous system is vulnerable to pharmacologic intervention. These are the ganglionic synapsis and the terminal fibers of the postganglionic nerves. Centrally the situation is more complex, and precise localization of the site of action of a drug is complicated by the interplay of both direct and indirect stimulatory and inhibitory actions on various centers.

Adrenergic Blockade

It has been known for many years that ergotoxine is able to reduce the pressor and other augmentory effects of either epinephrine or norepinephrine when injected before these amines. Other actions of ergotoxine, including a strong vasoconstrictor action of its own, militated against its use as a possible hypotensive agent. It was logically presumed that a norepinephrine antagonist lacking any vasoconstrictor action of its own might be employed to advantage in normalizing the elevated peripheral resistance associated with essential hypertension. This hope has never fully been realized, however. The naturally occurring alkaloid, yohimbine, an effective antagonist of norepinephrine, was not a vasoconstrictor, but unfortunately its central stimulant properties were sufficiently marked to approach convulsive levels.

The mechanism of action of the adrenergic blocking substances appears to be based on a competition with catecholamines for a binding site on the receptor substance of the vascular smooth muscle cells or of corresponding cells in other effector organs. The antagonism appears to be competitive and reversible in the case of certain substances such as phentolamine and piperoxan but is essentially irreversible in the case of dibenamine, apparently because of its firmer binding with the receptor substance.

Unfortunately, sympathetic cardioaccelerator activity is not impeded by any of these substances. On the contrary, there is a tendency to produce tachycardia, possibly because of the sparing of catecholamines at other sites.[10] The fact that such peripherally acting substances have been uniformly disappointing in the alleviation of essential hypertension provides supportive evidence that the etiology of this disorder is not regularly linked with excessive blood levels of sympathetic neurohumoral substances. An interesting pharmacologic application has been found for phentolamine which has been of value in the diagnosis and temporary palliative treatment of a pheochromocytoma, an adrenal medullary tumor producing epinephrine or norepinephrine in excessive amounts. Reduction of the hypertension associated with this condition by phentolamine is a valuable diagnostic point depending upon antagonism of the pressor effect of the high levels of circulating endogenous amines.

Ganglionic Blockade

The ganglionic blocking agents are a group of compounds which prevent the passage of nervous impulses through autonomic ganglia acting by a competitive antagonism with acetylcholine at that site. This group of substances are quaternary ammonium compounds or amines and include tetraethylammonium chloride, hexamethonium, chlorisondamine, pentapyrrolidinium, mecamylamine and others. These are not selective in their action, affecting parasympathetic and sympathetic ganglia alike. As a result of the blockade of sympathetic ganglia, the peripheral resistance is lowered and systemic blood pressure falls. Fortunately, the cardioaccelerator pathways are also blocked, preventing reflex tachycardia. Interestingly, the reactivity of the blood vessels to the catecholamines is increased during ganglionic blockade. There has been some question as to the mechanism of this potentiating effect. Since the basal systemic blood pressure is lowered, there can naturally be a greater absolute pressor effect following a maximally effective dose of a catecholamine which is capable of causing complete vasoconstriction. However, even with submaximal doses of the catecholamines, the absolute height of the pressor spike is commonly higher following blockade

of the ganglia, suggesting true potentiation.

Various explanations have been offered for this heightened effect. It has been attributed to the dampening of compensatory cardiac vagal reflexes or to increased reactivity of the blood vessels to the catecholamines such as is commonly seen in sympathetically denervated tissues. Both mechanisms may be operative. In any case, it would appear that if the latter medium is of importance, the normal circulating levels of the catecholamines are not sufficient to interfere with the characteristic hypotensive effect of ganglionic blocking agents. It is of interest in this regard, as Maxwell et al.[11] have shown, that this class of compounds, even in doses which produce marked falls in blood pressure in experimental animals, does not cause complete ganglionic blockade or denervation as evidenced by strong pressor responses upon splanchnic nervous faradization.

It must therefore be concluded that, although the ganglionic blocking agents are capable of altering the reactivity of the blood vessels to catecholamines, there is no evidence that this action is important for their observed antihypertensive effect.

Hydralazine

Historically, hydralazine was the next antihypertensive agent following the ganglionic blocking drugs to assume therapeutic prominence. This also has an influence on the reactivity of the blood vessels to the catecholamines, reducing their responsiveness to epinephrine and norepinephrine.[12] Its action in this respect resembles that of the adrenergic blocking agents but is somewhat milder, at least in acute experiments. As with adrenergic blocking agents, tachycardia occurs in acute experiments. The hypotensive effect of hydralazine had first been ascribed to an action within the central nervous system. However, it later became apparent that peripheral actions played the chief role in its action.

In addition to the adrenergic blocking effect already mentioned, hydralazine in amounts of about 20μg. has been shown to have a direct coronary dilating effect upon the isolated cat's heart. In the Starling heart-lung preparation of the dog, hydralazine has a dual effect, apparently dilating coronary arteries directly and also augmenting the vasodilator effect of epinephrine upon these vessels. It is possible that the apparently direct coronary dilator effect of hydralazine may be due to the potentiation of the catecholamines which Raab[13] has shown to occur so abundantly in cardiac tissue. Although there is no direct evidence that hydralazine dilates the renal vasculature, Reubi[14] has demonstrated an increased renal blood flow in the face of a reduced systemic blood pressure. It appears not unlikely, therefore, that a portion of the clinically observed antihypertensive action of hydralazine may be related to its property of increasing the responsivity of the vasculature to the sympathetic vasodilator component as suggested by Wilkinson.[15]

Reserpine

The first use of reserpine as an antihypertensive substance followed closely upon that of hydralazine. In 1953 Bein[16] reported the quieting action and the more subtle hypotensive action of reserpine, an alkaloid obtained from rauwolfia by Müller, Schlittler and Bein in 1952.[17] These results, which were confirmed by Plummer et al. in 1954,[18] were clearly recognized by both groups of workers as being consistent with a dampening of the influence of the sympathetic nervous system. Evidence presented at that time strongly suggested that the circulatory effects of reserpine, including hypotension accompanied by bradycardia and generally depressed pressor reflex activity, were consistent with a depressant action upon central sympathetic centers. This thesis was supported by the observation that the action potentials of the preganglionic cardioaccelerator fibers were reduced concurrently with the development of bradycardia.[19] Further support was afforded this concept when it was observed that the pressor response to elevated intracranial pressure was not suppressed, particularly since the mediation of such pressor function was situated at a medullary level below that of the sympathetic centers.

In 1955 Pletscher, Shore and Brodie[20] made the interesting observations that reserpine caused the liberation of serotonin from its binding sites at various locations in the body and especially from the central nervous system. It was suggested that this serotonin-depleting action of reserpine was related to its hypotensive and quieting actions. However, the observation by Holzbauer and Vogt[21] that reserpine also depleted norepinephrine from both hypothalamic and peripheral sympathetic nervous structures raised the question of the importance of the depletion of this catecholamine with known

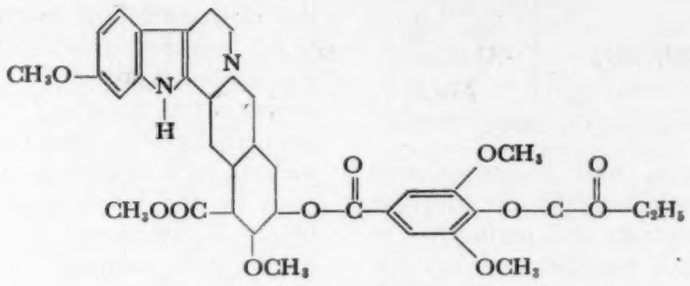

FIG. 1. Syrosingopine.

neurohumoral activity for the ability of reserpine to lower blood pressure. It has since become apparent that this latter effect is probably more important, since it has been shown by Carlsson et al.[22] and by Muscholl and Vogt,[23] as well as by Burn and Rand,[24] that the vasoconstrictor activity of the peripheral sympathetic nervous system is diminished as the catecholamines are depleted from the brain, heart, adrenal medulla and blood vessels, and from the peripheral sympathetic nerves and ganglia. Moreover, Burn and Rand have shown that the reduced contractility of isolated blood vessels depleted of their norepinephrine content by reserpine is restored to normal by the addition of norepinephrine to the perfusate. Maxwell et al.[25] have also provided pharmacologic evidence for the release by reserpine of a sympathetic neurohumoral agent, which produced in the dog a contraction of the denervated nictitating membrane which had been relaxed by removal of the ipsilateral superior cervical sympathetic ganglion. Of importance from a mechanistic standpoint, phentolamine promptly antagonized the contraction. The normal contralateral nictitating membrane, meanwhile, was relaxed as usual by administration of reserpine. It has also been observed that administration of reserpine caused a pressor response in animals in which the pathway between the brain and the periphery is interrupted by either ganglionic blockade or transection high in the cervical cord. Since this pressor effect is eliminated by the administration of phentolamine, a similar mechanism as mentioned leading to increased circulating catecholamines as well as to increased reactivity to these amines is the most likely cause of the pressor effect of reserpine.

The administration of epinephrine or norepinephrine intravenously to a reserpinized dog leads to an exaggerated pressor effect which is probably related to the increased sensitivity of the blood vessels which are in a sense "denervated" through the loss of norepinephrine from the nerves which innervate them. In this connection Burn and Rand[24] have demonstrated increased *in vitro* sensitivity of reserpine-treated blood vessels to administration of norepinephrine.

Krayer[26] has established that the catecholamines of the heart are released by administration of reserpine in the Starling heart-lung preparation and that the released amines give rise to a tachycardia, thus providing an explanation for this somewhat surprising occurrence in view of the bradycardia normally seen in the intact animal.

Neither hypertension nor tachycardia are common in the clinical use of reserpine because it is probable that the depletion of norepinephrine is gradual rather than precipitate with the small doses necessary for clinical antihypertensive activity. It is also probable that the central sympathetic dampening action of reserpine is an important part of the antihypertensive mechanism in the human.

The primary alteration, therefore, which is responsible for the hypotensive action of reserpine is the depletion of the catecholamine neuroeffector substance from the brain and peripheral sympathetic nerves, all alterations in the reactivity of the blood vessels to catecholamines being secondary to this depletion.

SYROSINGOPINE

The recent advent of a new antihypertensive substance known as syrosingopine (Fig. 1), a synthetic modification of reserpine,[27,28] has provided some insight into the matter of the relative importance of the release of serotonin and catecholamines for lowering the systemic blood pressure.

This substance alone, of more than a hundred modifications of reserpine or of the several naturally occurring esters of methyl reserpate,[29] exhibited predominantly hypotensive action with minor quieting activity. In the dog, for

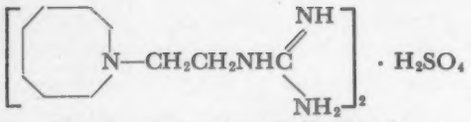

FIG. 2. Guanethidine (Su-5864).

example, syrosingopine and reserpine had equal hypotensive activity while the sedative effect of syrosingopine was one-tenth that of reserpine. It was thus possible to lower the blood pressure without attendant drowsiness. Hughes and Finger[30] have shown in the rabbit and dog that at effective hypotensive doses this compound caused marked depletion of peripheral cardiac catecholamines and moderate reduction of brain catecholamines, but no significant lowering of levels of brain serotonin. It thus appears that the hypotensive action of this substance, and probably of reserpine as well, is intimately linked with their effects upon catecholamines rather than upon serotonin. The observations of Garattini[31] have also implicated the release of catecholamines and not serotonin as an essential link in the cardiovascular effects of syrosingopine. A word is necessary, however, concerning the importance of the levels of reserpine itself in the brain for its observed actions. Sheppard et al.[32] have shown the presence of reserpine in brain for periods of seventy-two hours after a single injection of 100 μg. per kg. This observation suggests that the altered biochemical states responsible for the action of reserpine do not necessarily persist in the absence of significant tissue levels of reserpine.

GUANETHIDINE (SU-5864)

Another synthetic compound of a completely new and unique type pharmacologically, known as guanethidine (Su-5864) (Fig. 2), has been shown by Maxwell, Mull and Plummer[33] to modify the reactivity of the blood vessels to administration of catecholamines and to sympathetic nervous stimulation. Vascular reactivity to the injected amines is enhanced while the effects of nervous stimulation are markedly diminished.

Clinical studies of guanethidine by several investigators including Page and Dustan,[34] Frohlich and Freis[35] and Richardson and Wyso[36] indicate its beneficial influence on hypertension in human patients.

As with ganglionic blocking agents and reserpine, the pressor effect following carotid occlusion in the anesthetized dog is diminished. Following the oral or intravenous administration of guanethidine, a gradual drop in systemic blood pressure persisting for three to seven days is produced in the dog. Interestingly, the blood pressure fall produced by administration of guanethidine is considerably greater in the animal with neurogenic or renal hypertension than in the normotensive animal. This attribute is, of course, a potential asset in antihypertensive therapy. There is no sedative component associated with the hypotensive action of guanethidine.

The mechanism of the hypotensive action of this compound is based on its interference with sympathetic efferent transmission. After administration of guanethidine there was a two-stage effect. First there was evidence of sympathetic stimulation, including contraction of the nictitating membrane and piloerection in the cat. Within a few hours, however, there was a transition to a second stage of reduced sympathetic dominance characterized by relaxed nictitating membranes, hypotension and a reduced pressor response to carotid occlusion. In this latter stage there was no interference with the passage of impulses through the superior cervical ganglion. Nevertheless, the nictitating membrane contracted slightly or not at all to stimulation of either the pre- or postganglionic fibers of the superior cervical ganglion. The membrane actually was hyperresponsive to the effect of intravenously administered norepinephrine at this same time. At this stage also, the faradization of the splanchnic nerve or of the celiac ganglion was followed by very weak pressor spikes while the pressor responses to intravenous administration of norepinephrine were augmented above control. This combination of effects pointed to an interference with the transmission of impulses from the terminal or postganglionic sympathetic nerves to the effector cells by interfering with the availability of norepinephrine in some manner.

It is to be emphasized that administration of guanethidine does not cause peripheral adrenergic blockade. On the contrary, when administered after an adrenergic blocking agent such as phentolamine, a most interesting action is exhibited by guanethidine—the reduced norepinephrine-induced response is reverted to normal while reversal of epinephrine persists. The early sympathetic-like activity suggested a period of active catecholamine release comparable to that seen with reserpine. Preliminary evidence has been obtained by Sheppard*

* Personal communication.

in our laboratories to the effect that the catecholamine content of the rat's heart is reduced by half within two hours following the administration of guanethidine, providing presumptive evidence that the reduced responsivity of the blood vessels to the catecholamines normally liberated by the sympathetic nerves may be on the basis of a depletion of the neurohumoral mediator substance. Their increased sensitivity to norepinephrine would be consistent with the "denervated" state secondary to depletion of the sympathetic neurotransmitter. Since the action of guanethidine is distal to autonomic ganglia, it has no direct effect on the parasympathetic nervous system, and thus lacks most of the side effects associated with ganglionic blockade.

Sulfonamide Diuretics

The sulfonamide diuretics, chlorothiazide and hydrochlorothiazide, have been shown clinically by Wilkins,[37] Freis,[38] Hollander[39,40] and many others to possess antihypertensive properties. The mechanism of this action is not a direct one and is not immediately apparent. Barrett[41] did not obtain evidence of any significant drop in blood pressure in dogs when relatively large doses of these substances were administered acutely or smaller doses were administered chronically but did observe a suppression of the pressor action of norepinephrine by administration of hydrochlorothiazide. Gross[42] has shown that the pressor effects of norepinephrine and hypertensin are antagonized by administration of hydrochlorothiazide and that the depressor effect of chlorisondamine is accentuated; Barrett et al.[41] have found that administration of hydrochlorothiazide intensifies the hypotensive effect of hydralazine and histamine. It thus appears that hydrochlorothiazide may owe much of its reported antihypertensive effect to altering the reactivity of the vasculature to norepinephrine and other biologically active endogenous substances. In this connection it should be noted that Wilkinson et al.[15] have postulated that the antihypertensive action of hydralazine is due to sensitization of the vasodilators influenced by epinephrine.

The ultimate mechanism whereby the hypotensive activity of the sulfonamides is effected may still be related to their specific action of decreasing the resorption of sodium by the renal tubule. In 1950 Raab[43] demonstrated the greater pressor effect of adrenergic substances in human beings treated with desoxycorticosterone with and without increased sodium intake. Silva and Croxatto[44] made a similar observation in rats. Gross and Lichtlen[45] recently noted a heightened sensitivity of rats pretreated with desoxycorticosterone and sodium not only to administration of epinephrine and norepinephrine but also to administration of renin, hypertensin and vasopressin. One possibility suggested by Gross for these observations is an increased sensitivity of the arterial system to hypertensive stimuli due to a higher sodium, potassium and water content of the arterial wall. Objective support for this thesis has in fact been provided by Tobian and Redleaf[46,47] and by Williams,[48] who showed that administration of desoxycorticosterone and overdosage of sodium increased the water, sodium and potassium content of the aorta of the rat in desoxycorticosterone-induced hypertension, in adrenal regeneration hypertension and in the hypertension which persists following the removal of an ischemic kidney of the rat. Significantly, Renzi et al.[49] have shown that administration of hydrochlorothiazide ameliorated the hypertension associated with adrenal regeneration in the rat, while Gross[42] also found a retardation of "desoxycorticosterone hypertension" induced in rats by administration of hydrochlorothiazide. Significantly, hydrochlorothiazide is not effective against hydrocortisone-induced or renal hypertension in the rat, probably because these conditions are not dependent upon increased sodium in the diet.

Though the etiology of essential hypertension remains uncertain, there is evidence that a defect in electrolyte excretion commonly becomes manifest at some point in its course. At such a time the changes in vascular composition and reactivity mentioned above might ensue, and, as a result, lead to further peripheral resistance due to "water logging" of the arterioles as proposed by Tobian et al.[47] In this connection, Mendlowitz and Meyer[50] have also shown that the size of the lumen of the arterioles in the fingers of hypertensive patients is decreased when compared to normotensive control subjects following blockade of the digital constrictor nerves. Similarly, Folkow[51] has noted greater vascular resistance in hypertensive patients than in normal subjects when maximal vasodilation had been achieved.

On the basis of the evidence presented, it may reasonably be suggested that hydrochlorothiazide exerts its antihypertensive effect, at least in part, by combatting the tendency for an ac-

cumulation of fluid and electrolytes in arterial walls, thus reducing their responsivity to the constrictor influence of catecholamines and other pressor substances.

Comments

The primary physiologic aberration associated with essential hypertension is an elevated peripheral resistance based on an arteriolar narrowing of uncertain etiology. Logically, efforts in the development of antihypertensive drugs have been focused upon substances capable of restoring the elevated vascular resistance toward normal. It has become apparent that the most fruitful course of endeavor has been the utilization of agents which dampen the control exerted by the sympathetic nervous system upon the arterioles. This attribute alone, however, is not adequate to insure satisfactory antihypertensive action, as witnessed by the inadequacy of the classic adrenergic blocking drugs in this regard. Nevertheless, all of the effective antihypertensive agents have the common property of altering the reactivity of blood vessels to the action of both endogenous and exogenous catecholamines and, most commonly, the effects on the amines of these two different origins are in opposite directions. The reduction of the effect of the endogenous amines, especially that of norepinephrine, upon the blood vessels appears to be the more important criterion in the delineation of antihypertensive action of clinical utility. This conclusion is supported by the fact that the ganglionic blocking agents, hydralazine, reserpine, syrosingopine and guanethidine, share the common property of diminishing pressor reflexes, typified by the carotid occlusion reflex, which are mediated by the sympathetic nervous system. The reverse or augmentory effect which each of these substances, with the exception of hydralazine, exerts upon the pressor influence of exogenous norepinephrine would be expected to cause an elevation rather than a lowering of the blood pressure. It is likely an artefact which would occur but infrequently under usual physiologic conditions under which the antihypertensive agent is administered exogenously while the norepinephrine is produced endogenously at specific regions of the sympathetic nervous system.

There is evidence also that the sulfonamide diuretics such as hydrochlorothiazide may exert their clinically reported antihypertensive action by reducing the reactivity of the blood vessels to catecholamines either directly or possibly in the hypertensive state by restoring the sodium content of the plasma and the blood vessel walls toward normal values.

Since the various agents under discussion accomplish their antihypertensive effects in several distinct ways, optimum results are frequently achieved by the adaptation of combinations of substances selected so as to augment the desirable and minimize the undesirable attributes of each. This comprehensive armamentarium of potent and specific agents which has become available within the past decade has provided a challenge, but great benefits as well, when utilized to best advantage.

Summary

Although definitive evidence is lacking that autonomic overactivity bears any direct relationship to the genesis of essential hypertension, a diverse group of antihypertensive substances, including ganglionic blockers, hydralazine, reserpine, syrosingopine and guanethidine, share the property of reducing the magnitude of the rise in blood pressure elicited by reflexly induced sympathetic nervous vasoconstriction. By contrast, these same substances, with the exception of hydralazine, which exhibits mild adrenergic blocking action, enhance the pressor activity of exogenously administered norepinephrine. On this basis it is suggested that interference with the elaboration of norepinephrine or with the vasoconstrictor effect of endogenously produced norepinephrine may be of considerable importance for the observed antihypertensive actions of the above mentioned compounds.

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The Nature of the Increased Peripheral Resistance in Hypertension*

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ALTHOUGH it has long been known that the elevation of blood pressure in hypertension is the result of increased peripheral resistance, the means by which this abnormality occurs has not been established. It has generally been assumed that it is due to an increase in muscle tone but the absence of a method for measuring the degree of vasomotor tone has made it impossible to verify this.

VASOMOTOR TONE

In any vascular bed there are two variables governing the relation between pressure and flow. The first is the basic structure of the vascular tree supplying the area, that is, the number of blood vessels and their cross-sectional area. The second is the degree to which the smooth muscle in these vessels is actively contracting to produce what is known as tone. That the blood flow depends on these two variables is demonstrated in Figure 1, which shows the pressure-flow curves obtained from the hind limbs of two dogs. The two preparations in the denervated state had approximately the same rate of blood flow but in one of them (left) the removal of vascular smooth muscle tone by an intra-arterial infusion of supramaximal doses of acetylcholine led to a twentyfold increase in

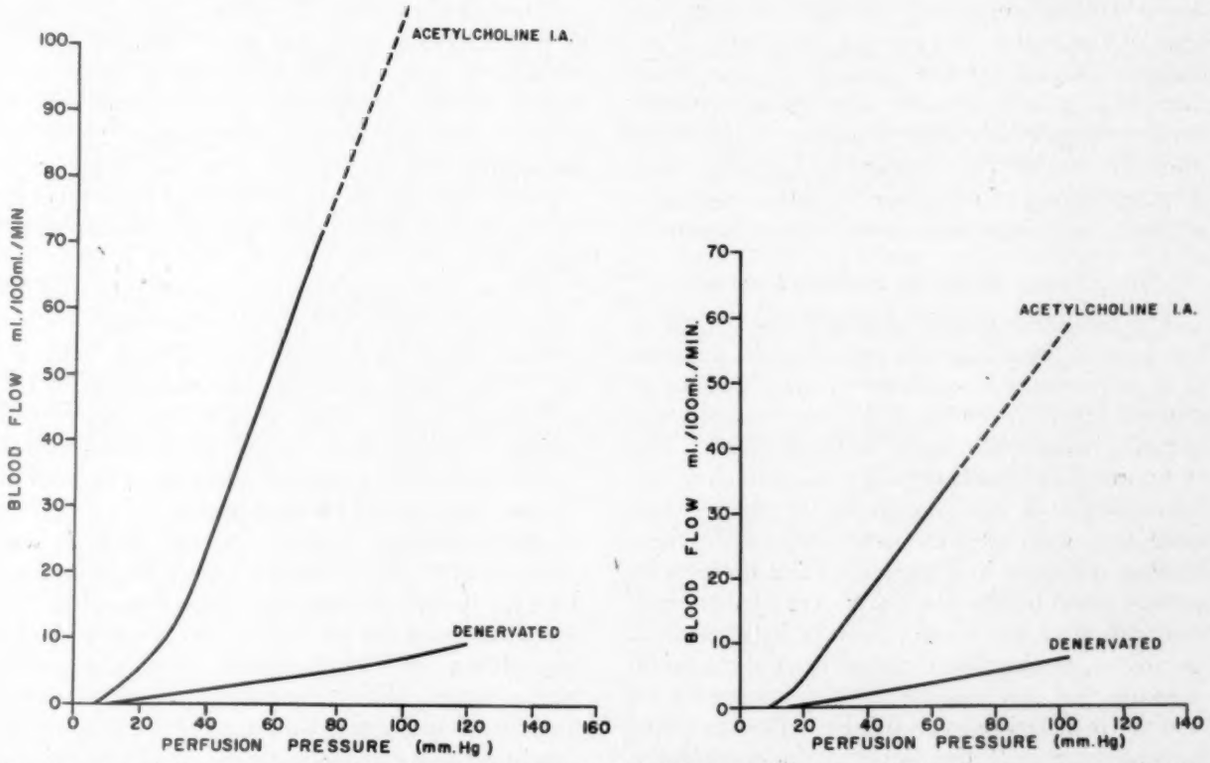

FIG. 1. Pressure-flow curves obtained from the denervated hind limb of two dogs with similar flow rates. Note the difference in flow after maximal dilation of the bed by acetylcholine. See text.

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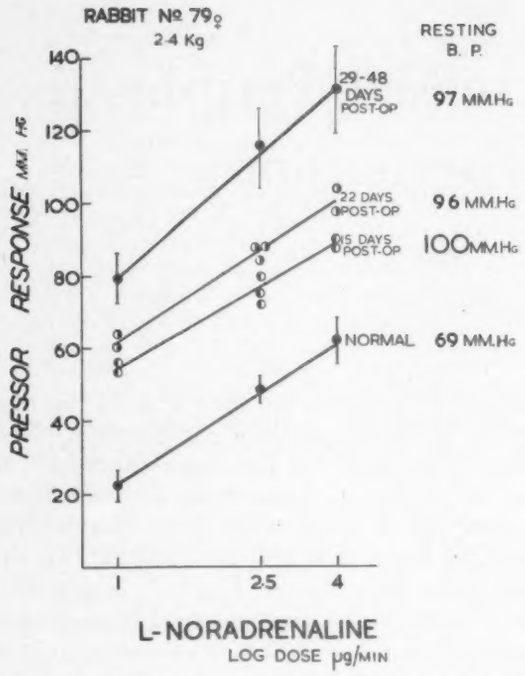

FIG. 2. Repeated dose response curves to norepinephrine in a rabbit in the normal state and again after the development of hypertension. Each study was performed after the animal had been given a large dose of hexamethonium.

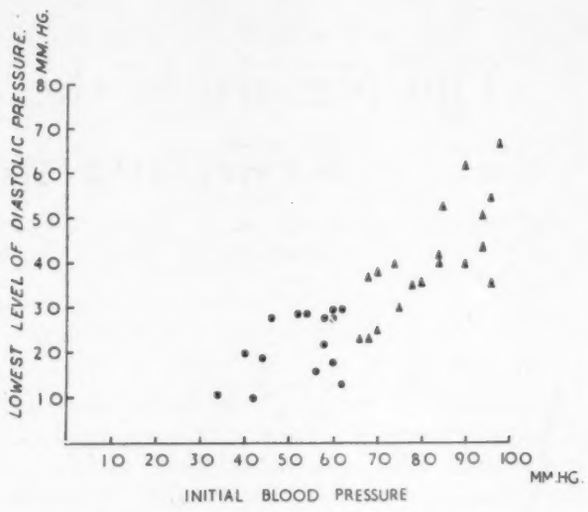

FIG. 3. Structural resistance and hypertension. The lowest level of blood pressure produced by supramaximal intravenous doses of nitroglycerin in eight rabbits before and after the development of renal hypertension. ● = normal. ▲ = after operation for the production of hypertension.

flow. In the animal shown on the right, release of vasomotor tone led to a much smaller increase. In the second preparation, therefore, there was a large element of residual or structural resistance, whereas vascular smooth muscle played a smaller part in the regulation of flow. The separation of these two variables in hypertension has never been satisfactorily achieved.

STRUCTURAL FACTORS IN HYPERTENSION

The possibility that structural factors might be involved in the changes in resistance in the state of hypertension was suggested by a study of the increased reactivity to administration of catecholamines in animals with hypertension.[1] The response of the blood pressure in a rabbit to administration of norepinephrine in the normal state and again after the development of hypertension is shown in Figure 2. The increase in pressor effect occurs gradually over the course of a month after the development of hypertension, during which time the elevated level of the blood pressure has not changed. The increased reactivity is therefore not a passive reflection of the hypertensive state but develops independently. Further investigation of this phenomenon revealed that it was not confined to norepinephrine but was a non-specific response to many pressor agents and also to depressor drugs.[2,3] It was also found that the duration of the response to administration of norepinephrine or nitroglycerin was not prolonged in the hypertensive state as might be expected if there were a true increase in sensitivity of vascular muscle to these drugs. Injection of nitroglycerin provided further interesting and unexpected results in animals with hypertension. However large the dose of nitroglycerin, the blood pressure could never be reduced to the same level in hypertension as it could in the normal state[4] (Fig. 3).

These results suggested the possibility that increased reactivity in hypertension could be explained on a mechanical basis if there were an increased thickness of the internal layers of the arteriolar wall. This would give increased vascular responses to drugs, yet it would be a non-specific effect and the duration of the action of the drugs would be unchanged.

Plethysmographic Studies: At this time it was demonstrated by Folkow[5,6] that in hypertension in human beings the blood vessels of the forearm could not be dilated to the same extent in patients with hypertension as in normotensive subjects. Since the concept of an increased structural resistance would have an important bearing on our understanding of the nature of hypertension, further investigation of this possibility has been undertaken in eleven normal subjects and twenty-seven patients with hyperten-

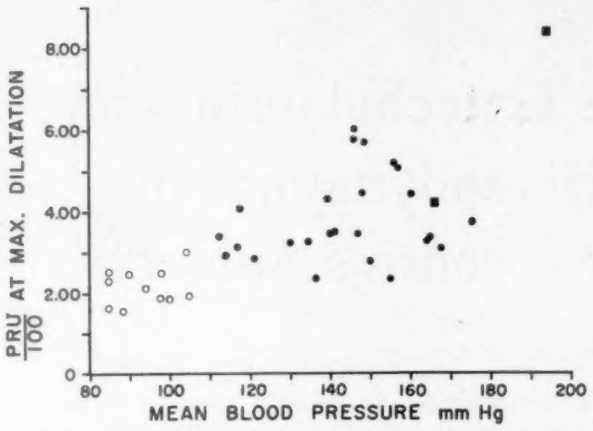

FIG. 4. Structural resistance and hypertension. The relationship between blood pressure and minimal structural resistance in the forearm vessels of normal subjects and patients with hypertension. Structural resistance, measured after maximal dilation, has been produced in the forearm vessels by exercise and ischemia of eight minutes' duration. ○ = normal subjects. ● = essential hypertension. ■ = renal hypertension.

sion. Blood flow in the forearm was measured by a Whitney strain gage plethysmograph[7] after maximal dilation was produced by exercise and ischemia of eight minutes' duration. The greatest blood flow recorded after ischemia, taken with the level of blood pressure, gave the structural resistance. The mean resistance in the normal subjects was 2.20 peripheral resistance units per 100 cc. of tissue, whereas only 2 patients with hypertension had this level. The relation between the structural resistance and the severity of hypertension is shown in Figure 4. Thus it can be seen that the structural resistance rises roughly in proportion to the level of blood pressure.

It is possible that this increased structural resistance is the consequence of hypertension and not associated with its initiation. If this were so the structural changes demonstrated here would be an indication of the accelerated arteriosclerosis associated with hypertension. Preliminary studies, however, show that the development of structural changes in hypertension is not a continuing process, since there is no demonstrable association between the level of structural resistance and the duration of hypertension.

SUMMARY

Studies on hypertension in both human beings and animals have shown an increased response to vasopressor and vasodepressor agents. This increased reactivity, as well as the incompleteness of vasodilatation by large doses of vasodepressor agents, is believed to be due to structural changes in the vascular tree. Plethysmographic studies have demonstrated an increased structural resistance in blood vessels of the forearm in patients with hypertension as compared with normal subjects.

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The Effects of Various Catecholamines on Specific Vascular Hemodynamics in Hypotensive and Normotensive Subjects*

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WHILE elimination or correction of the cause of shock is theoretically and often the ideal method of treatment, the judicious use of vasopressor drugs is often indicated, and indeed often required even when adequate measures have been carried out to correct the etiology of the shock (for example, blood transfusion in hemorrhagic shock). When selecting a drug to raise the blood pressure, consideration must be given not only to its potency and duration of action, but also to the site and nature of it action, since it appears that there are differences in the capacity of these agents to react with adrenergic receptors in one vascular bed as compared to another. Aside from this factor there also are differences in the effects of these agents on myocardial function and cardiac output. The observations herewith reported were carried out over a period of several years and are representative of the results obtained in a large number of subjects, both animal and human.

METHODS

The catecholamines used are shown in Figure 1, and except for isopropylarterenol, which was used to study the vasodilator effects of this class of compounds, and epinephrine, all have been commonly used clinically in the treatment of shock. The methods of administration varied depending on the nature of the study and are noted in the section on results. *In the experiments on dogs*, the animals were anesthetized with sodium pentobarbital, 25 mg./kg., and determination of glomerular filtration rate was made from the clearance of exogenously administered creatinine. Renal plasma flow was calculated from the clearance of p-amino hippuric acid. *In the human subjects*, glomerular filtration rate was measured using the clearance of inulin, and renal plasma flow from the clearance of p-amino hippuric acid. In both dogs and human subjects, standard clearance technics were used as outlined in previous communications.[1,2] Cerebral blood flow was measured by the technic of Kety and Schmidt.[3]

RESULTS

EFFECTS ON RENAL HEMODYNAMICS

Normotensive Subjects: Figure 2 depicts the effects of the administration of six different sympathicomimetic agents on renal hemodynamics in normotensive dogs.[1] In these experiments, dosage of the drug was determined by the animal's response, i.e., an attempt was made to obtain a certain blood pressure response rather than to give a fixed amount of the drug. Control values were represented as 100 per cent, and the per cent change calculated from the values obtained during the period of drug administration. Clearances were measured at two blood pressure levels for each drug, the first represented by the height of the open bars and the second by the height of the cross

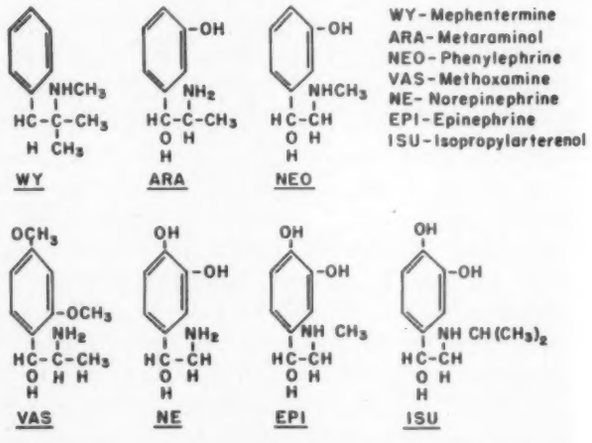

FIG. 1. Structural formulas of sympathicomimetic drugs investigated.

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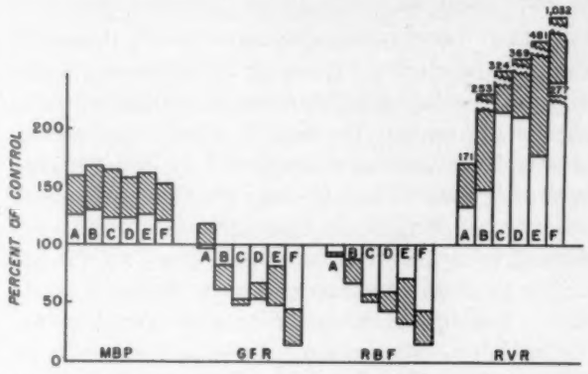

FIG. 2. Comparison of effects of administration of six sympathicomimetic drugs on renal hemodynamics in normotensive dogs. Open and hatched bars represent values at two different levels of blood pressure response (see text). MBP = mean blood pressure. GFR = glomerular filtration rate. RBF = renal blood flow, RVR = renal vascular resistance. A = mephentermine (Wyamine). B = metaraminol (Aramine). C = phenylephrine (Neo-Synephrine). D = norepinephrine (Levophed). E = epinephrine. F = methoxamine (Vasoxyl).

hatched bars. Although blood pressure response at the first or second level was similar in all groups, marked quantitative differences in renal hemodynamics occurred. Administration of mephentermine (Wyamine®) produced little change in glomerular filtration rate or renal plasma flow, but administration of methoxamine (Vasoxyl®) led to a marked reduction in these functions. Administration of the other drugs had intermediate effects. This suggested that methoxamine had a greater capacity to react with or stimulate renal adrenergic receptors

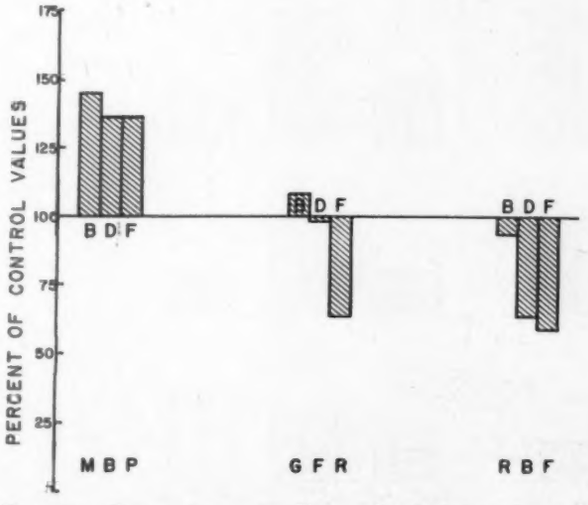

FIG. 3. Comparison of effects of administration of sympathicomimetic drugs on renal hemodynamics in normotensive human subjects. Abbreviations as in Figure 2.

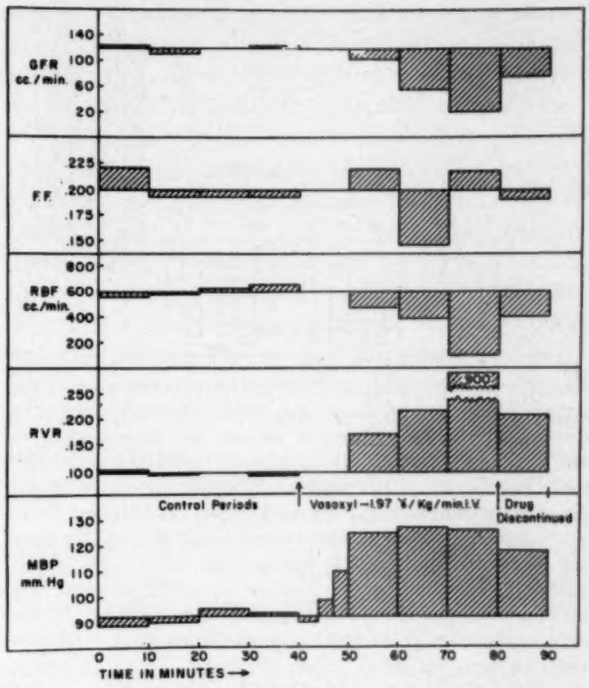

FIG. 4. Effects of administration of methoxamine on renal dynamics. F. F. = filtration fraction. RVR = renal vascular resistance. Other abbreviations as in Figure 2.

than the other agents when compared with their capacity to react with those in the systemic vasculature in general, the latter being judged by the rise in systemic blood pressure.

Similar results were also obtained when three of these drugs were given to normotensive human subjects[4] (Fig. 3). The effect of the administration of one of these drugs on renal function in a normotensive subject is shown in Figure 4.

Hypotensive Subjects: In subsequent experiments after determination of renal function during a control period, dogs were bled until the mean blood pressure was approximately 50 mm. Hg (Fig. 5). After stabilization, renal function was measured again and subsequently a vasopressor drug was given to raise the blood pressure to levels approximating those in the control period. During the period of shock before the sympathicomimetic amine was given, glomerular filtration rate and renal blood flow were reduced to 20 to 30 per cent of control values. After administration of the drugs, there was some improvement in function except in the group receiving methoxamine. In the groups given mephentermine, metaraminol (Aramine®) or phenylephrine (Neo-Synephrine®), renal vascular resistance decreased, indicating a relatively greater effect of these drugs on vascular

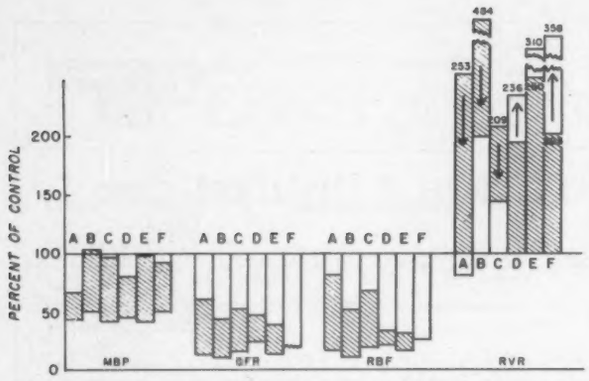

FIG. 5. Comparison of effects of administration of six sympathicomimetic drugs on renal hemodynamics in hypotensive dogs. Control values are represented as 100 per cent. Lower border of cross hatched bars represents values during the period of shock for mean blood pressure, glomerular filtration rate and renal blood flow, and upper border of cross hatched bars these values during administration of the vasopressor drug. For renal vascular resistance upper border of cross hatched bars indicates values during shock and the direction of the arrows the change during drug administration. Abbreviations as in Figure 2.

adrenergic receptors other than those in the renal vessels; in contrast, administration of the other three drugs led to a further increase in renal vascular resistance, indicating a greater effect on renal vascular adrenergic receptors.

The fact that administration of most of these drugs can cause an increase in renal blood flow in hypotensive subjects, while they cause a decrease when given to normotensive subjects, can be explained by the fact that there is disproportionately more renal vasoconstriction in shock than in the over-all systemic circulation. Consequently, when smaller doses of certain of these agents are given, the initial effect is to cause relatively more vasoconstriction in the general systemic vessels than in the renal vessels. This leads to an increase in blood pressure with a resulting increase in renal blood flow, as the increase in renal vascular resistance has been minimal. If larger doses are then given, renal vasoconstriction with some of the drugs proceeds at a faster rate than in the general systemic vessels, with a resulting decrease in flow. This is illustrated in Figure 6 which shows the effects of the administration of norepinephrine (Levophed®) on renal hemodynamics before and after hemorrhage. Here it can be seen that the drug, when given to the normotensive animal, led only to a decrease in glomerular filtration rate and renal plasma flow, whereas in the hypotensive state infusion of the drug to raise the blood pressure to normal led to an increase in glomerular filtration rate and renal plasma flow. Further elevation of the pressure to levels above normal again led to depression of these functions.

Although regional vascular changes are emphasized here, it should not be implied that other factors are not important when these drugs are given to hypotensive subjects. As will be discussed subsequently, increased venous

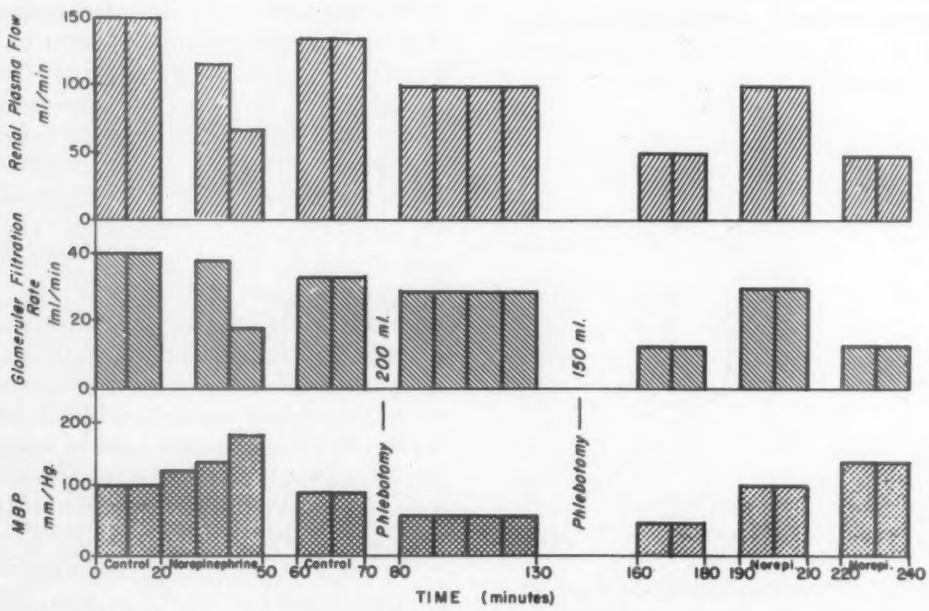

FIG. 6. Effect of administration of norepinephrine on renal hemodynamics before and after experimental hemorrhagic shock.

return and changes in cardiac output and blood viscosity are probably important in the total effect.

In human patients in shock it was more difficult to obtain comparative data regarding the effects of these drugs; however, the results shown in Figure 7 are consistent with the previous data. In this patient with shock due to blood loss both glomerular filtration rate and renal blood flow were markedly reduced prior to therapy. When blood pressure was elevated toward normal levels by administration of metaraminol, both glomerular filtration rate and renal plasma flow increased. During a subsequent period norepinephrine was given, and although the blood pressure was elevated to levels identical with those obtained during the period when metaraminol was given, there was less rise in glomerular filtration rate and renal blood flow. Subsequently the patient was given 1,000 ml. of whole blood; although the blood pressure response was good, renal function failed to improve as much as it had during infusion of metaraminol. This again would indicate that certain of the drugs, as exemplified here by metaraminol, have less effect on renal vasoconstriction than others in the group studied. The data also illustrate the fact that vasopressor agents are of value even in hypovolemic shock.

The mechanism by which some of these drugs cause a greater effect on renal hemodynamics than others has not been proved. Studies in which vasodilator activity has been measured after adrenergic blockade with phenoxylbenzamine show that epinephrine and isopropylarterenol are the only drugs in the group studied with marked vasodilator activity.[1] Norepinephrine and mephentermine have slight activity and the rest have no vasodilator effect under these conditions. The fact that both metaraminol and methoxamine do not possess vasodilator activity, but yet differ widely in their effects on renal hemodynamics, suggests that vasodilator activity of the sympathicomimetic amines is not primarily responsible for the differences of the effects of these compounds on renal hemodynamics.

Renal Artery Injection Experiments: These drugs have also been injected into one renal artery of dogs in which both ureters were catheterized so that renal function could be measured separately in each kidney. Those drugs which had the greatest effects on renal vasoconstriction when injected intravenously, also had a longer duration of action and caused more reduction in glomerular filtration rate and renal plasma flow when given into the left renal artery. Such an experiment is depicted in Figure 8. After a control period, 1 ml. of saline was injected into the left renal artery to serve as a control on effects from the injection technic itself. Methoxamine, 1 mg., was then injected into the artery over a one- to two-minute period. This produced marked vasoconstriction on the injected side. Phenoxybenzamine was then

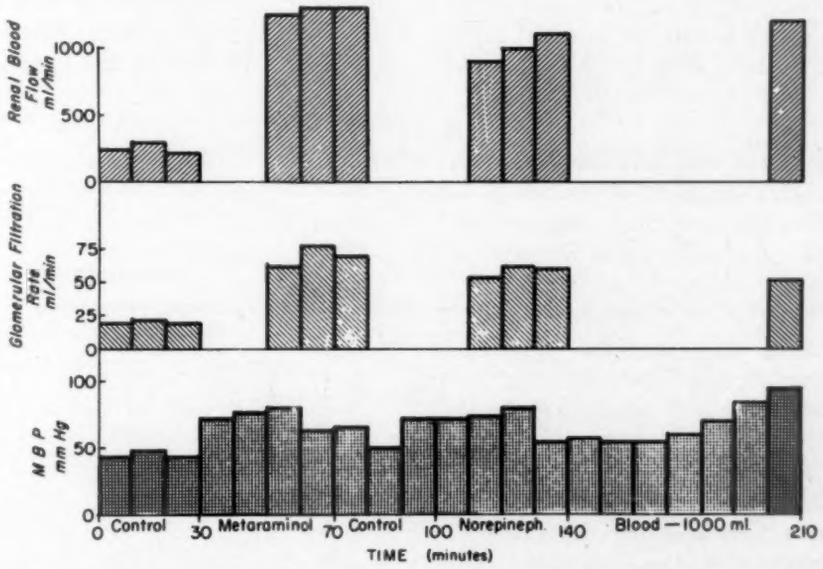

FIG. 7. Comparison of administration of metaraminol and norepinephrine and blood transfusion on renal hemodynamics in hemorrhagic shock in a human subject.

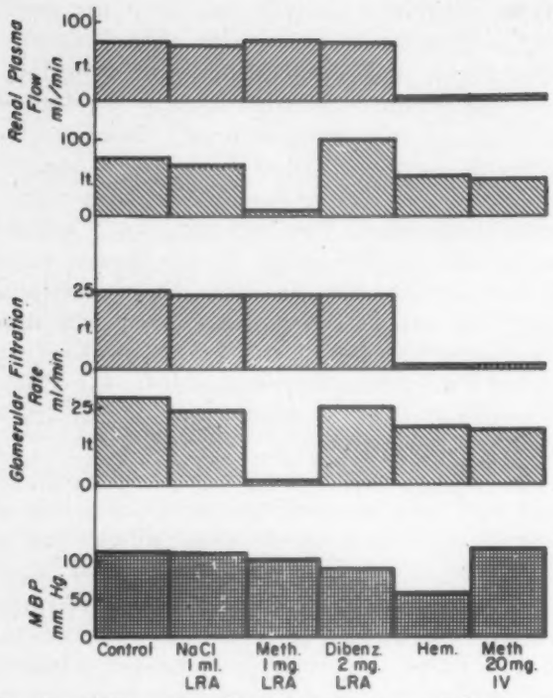

FIG. 8. Effects of unilateral renal artery injection of methoxamine on renal hemodynamics.

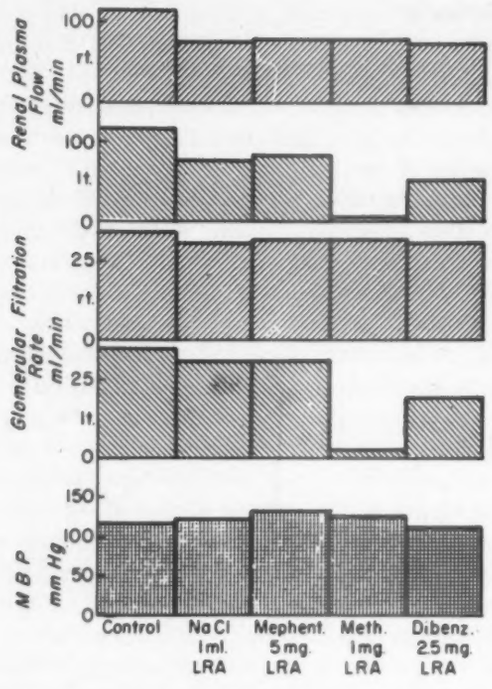

FIG. 9. Comparative effects of mephentermine and methoxamine on renal hemodynamics when given into one renal artery.

injected into the left renal artery, effectively blocking the methoxamine. Shock was then produced by bleeding. This caused marked reduction of glomerular filtration rate and renal plasma flow in the right kidney, but the left kidney was protected from endogenous sympathetic vasoconstriction by the phenoxybenzamine. The dog was then given methoxamine intravenously, and although blood pressure was restored to control levels, as in previous experiments there was no improvement in renal function in the right kidney, indicating that renal vasoconstriction had increased proportionately along with the rise in blood pressure.

Figure 9 shows a comparison between the effects of mephentermine and methoxamine when injected into the left renal artery of a dog. Mephentermine had no effect and methoxamine a marked effect. In other experiments not shown here norepinephrine had an intermediate effect when given by the same technic.

While other factors are involved in the total

TABLE I

Comparative Effects of Sympathicomimetic Drugs on Cerebral Hemodynamics in Normotensive Subjects*

Drug	Mean Blood Pressure	Cerebral Blood Flow	Cerebral Vascular Resistance	Cerebral Oxygen Uptake
		King et al.[5]		
Epinephrine	120	121	98	122
Norepinephrine	129	91	143	95
		Moyer et al.[6]		
Norepinephrine	124	88	153	95
Metaraminol	120	91	150	94

* All values are expressed as per cent of control; control is 100 per cent.

TABLE II

Comparative Effects of Metaraminol and Norepinephrine on Cerebral Blood Flow During Hypotension Due to Ganglionic Blockade*

Drug	Mean Blood Pressure	Cerebral Blood Flow	Cerebral Vascular Resistance	Cerebral Oxygen Uptake
Hexamethonium	61	66	94	100
Metaraminol	111	105	100	121
Hexamethonium	63	73	82	94
Norepinephrine	119	87	135	97

* Data from Moyer et al.[6] All values expressed as per cent of control.

response when these drugs are administered intravenously, the experiments in which renal artery injection was used serve to confirm the importance of the local vascular response in the mechanism producing differential effects on renal hemodynamics.

EFFECTS ON CEREBRAL HEMODYNAMICS

Less data are available concerning the comparative effects of the administration of sympathicomimetic drugs on cerebral hemodynamics. King et al.[5] and Moyer et al.[6] have studied the effects of three of these agents on cerebral blood flow in normotensive subjects. These results are summarized in Table I. In contrast to its effect on renal hemodynamics, administration of epinephrine increased cerebral blood flow; when norepinephrine and metaraminol were given, cerebral blood flow decreased slightly.

Metaraminol and norepinephrine were also given to subjects in whom hypotension was induced by ganglionic blockade (Table II). When blood pressure then was elevated to levels slightly above the control by administration of metaraminol, cerebral blood flow and cerebral oxygen consumption increased above control levels; when norepinephrine was given, cerebral blood flow increased, but not to normal levels. Cerebral vascular resistance increased above the control value during administration of norepinephrine, whereas it did not when metaraminol was given. These data again suggest that sympathicomimetic amines may have qualitatively or quantitatively different effects on a given vascular bed.

TABLE III

Effect of Norepinephrine on Cerebral Blood Flow in Hemorrhagic Shock

Procedure	Mean Blood Pressure (mm. Hg)	Cerebral Blood Flow (ml./100 gm./min.)
Shock	58	40
Norepinephrine	90	51
Norepinephrine	120	46
Control (after 1 week)	86	54

In Table III the effects of norepinephrine on cerebral blood flow of a patient in hemorrhagic shock are shown. In the untreated state cerebral blood flow was moderately reduced. After moderate elevation of the blood pressure by administration of norepinephrine, cerebral blood flow increased to a value subsequently found to be near this patient's normal level; however, after further elevation of the blood pressure to hypertensive levels, there was a reduction in cerebral blood flow, similar to that observed when this drug was given to normotensive subjects.

EFFECTS ON CARDIAC HEMODYNAMICS

Table IV shows the general effects of administration of these sympathicomimetic drugs on cardiac output, pulse rate, peripheral vascular resistance and coronary blood flow, the data being obtained by studies on normotensive human subjects and animals. No strictly comparable data are available which can be used to indicate quantitative differences. Even less information is available regarding their comparative quantitative and qualitative effects in hypotensive subjects, and it should be remembered that even in the normal subject, the net result of observed changes reflects the pharmacologic action of the drugs on many mechanisms governing cardiac hemodynamics other

TABLE IV
Effect of Sympathicomimetic Drugs on Cardiac Output and Coronary Blood Flow in Normotensive Subjects

Drug	Cardiac Output	Pulse Rate	Peripheral Vascular Resistance	Coronary Blood Flow
Mephentermine	Increase	Unchanged or variable	Increased, or unchanged or variable	Increased
Metaraminol	Unchanged or or variable	Decreased	Increased	Increased
Phenylephrine	Decreased	Decreased	Increased	Increased
Norepinephrine	Unchanged or variable, or decreased	Decreased	Increased	Increased
Epinephrine	Increased	Increased	Decreased	Increased
Methoxamine	Unchanged or variable, or decreased	Decreased	Increased	Increased

than an effect on myocardial contractility and coronary artery blood flow. For example, in shock, administration of norepinephrine (and other sympathicomimetic drugs as well) often increases cardiac output in contrast to the effect in normotensive subjects. Table v presents the results of such an experiment in an animal in which hypotension was effected by bleeding. After an initial control period, the dog was bled and cardiac output again measured and found to be reduced. When the blood pressure was then raised to slightly less than control values by administration of norepinephrine, cardiac output increased to the control level. The most likely mechanism for this effect in hemorrhagic shock is that the intense vasoconstriction produced by administration of norepinephrine forces blood out of small peripheral vessels and capillaries, thus leading to increased cardiac output.

TABLE V
Effect of Norepinephrine on Cardiac Output in a Hypotensive Dog

Procedure	Mean Blood Pressure (mm. Hg)	Cardiac Output (ml./sec.)	Peripheral Vascular Resistance (Mean blood pressure/ cardiac output)
Control	129	38	3.4
Shock	49	23	2.1
Norepinephrine	110	40	2.8
Transfusion	110	46	2.4

Even when coronary blood flow is reduced and the cause of the shock is cardiogenic, administration of sympathicomimetic agents may have a beneficial effect when used properly. Although no measurements of cardiac output were made, it is evident from Table VI that vasopressor therapy resulted in an appreciable increase in survival rate in myocardial infarction. Apparently even in this circumstance it is possible to increase cardiac output and coronary blood flow by such therapy.

TABLE VI
Effect of Norepinephrine on Survival in Myocardial Infarction with Hypotension*

Systolic Blood Pressure (mm. Hg)	No. of Patients	Per Cent Responding	Per Cent Survival	Survival Without Treatment (%)
0 to 40	25	72	20	9
40 to 80	31	97	45	15

* Combined results, Tainter et al.[7]; Moyer et al.[8]

Comments

The data reported here indicate that vasopressor drugs can be of definite value in the treatment of hypotension. Certainly, specific therapy should also be given to counteract the etiologic factors causing the shock, but even when this is carried out, vasopressor therapy may be necessary. In some instances, when the basic cause cannot be corrected immediately, as, for example, when infection or myocardial infarction are present, prolonged vasopressor therapy may be indicated.

Consideration should also be given to the physiologic status of the patient and the total pharmacologic spectrum of the sympathicomimetic drug to be used. It seems rather illogical to administer a drug which has pronounced renal vasoconstrictor activity to a patient who already has oliguria as a result of the shock; rather, an agent with minimal activity on these vessels should be selected. Unfortunately, enough data are not yet available regarding the effects of these drugs on other vascular systems such as the brain and heart during hypotension to allow a logical choice when there is evidence of severe ischemia to these areas. Further investigation, however, should permit such a selection.

It should also be emphasized that these agents are of definite value, even when shock is associated with diminished blood volume, and their use may be life-saving while waiting for blood to be typed and cross matched, and during the initial periods of its administration before the patient's blood volume has returned to normal. As noted, it is important to raise the pressure only to a point approximately normal for that patient, since elevation of pressure above this point is often associated with reduction in blood flow to vital areas, even though the initial response may have been an increase in blood flow.

Summary

Data are presented which indicate that all vasopressor sympathicomimetic amines do not act on the same regional vascular bed in the same manner. For example, administration of one amine may cause marked renal vasoconstriction in relation to general vasoconstriction, whereas another may cause only slight renal vasoconstriction. Preliminary evidence suggests that such differences may exist as far as cerebral vasculature is concerned. The data suggest that consideration should be given to the total pharmacologic action of a vasopressor drug rather than only to its potency in raising blood pressure.

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Studies on Vasoactivity of Catecholamines in Man*

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IT HAS BEEN customary to use systemic arterial pressure as the criterion for assessing the influence a chemical substance may exert upon vasomotion.[1–3] This approach has been widely used both in the animal experiment[4,5] and in clinical investigation,[6,7] for substances occurring in the mammalian body as well as for synthetic pharmacologic agents.

It has been generally recognized, of course, that various vascular beds may show directionally different responses to specific vasomotor stimuli.[2,8,9] Moreover, there has been growing

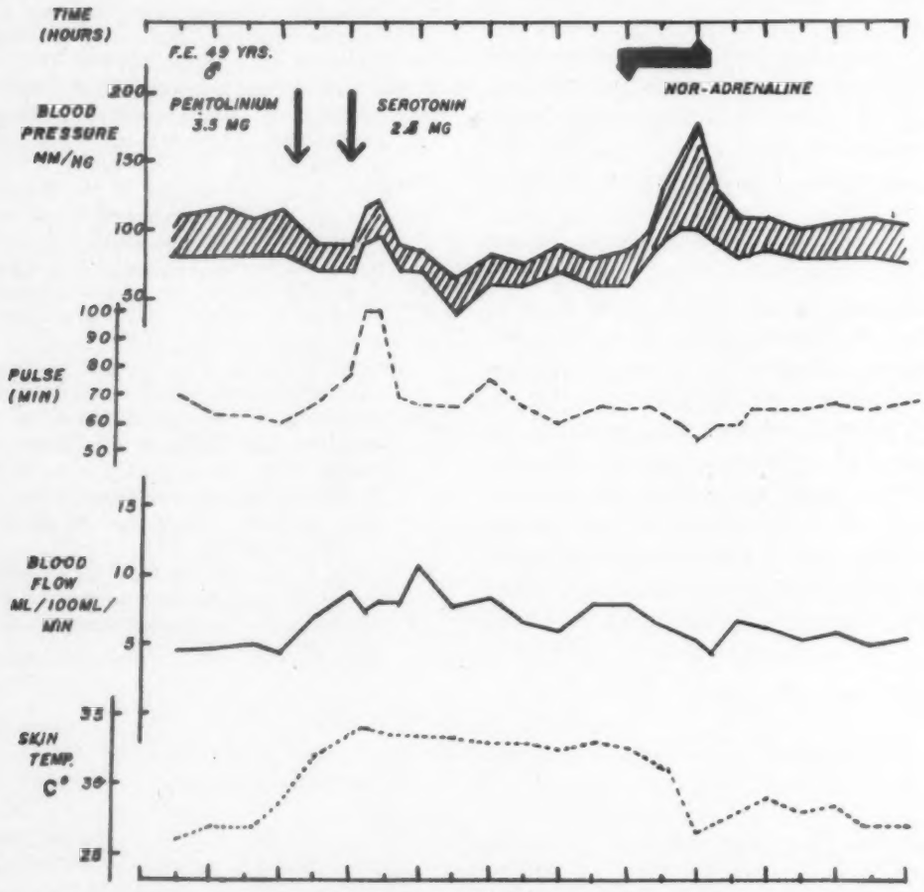

FIG. 1. Effects of administration of serotonin and noradrenaline in hypotension induced by pentolinium administration.

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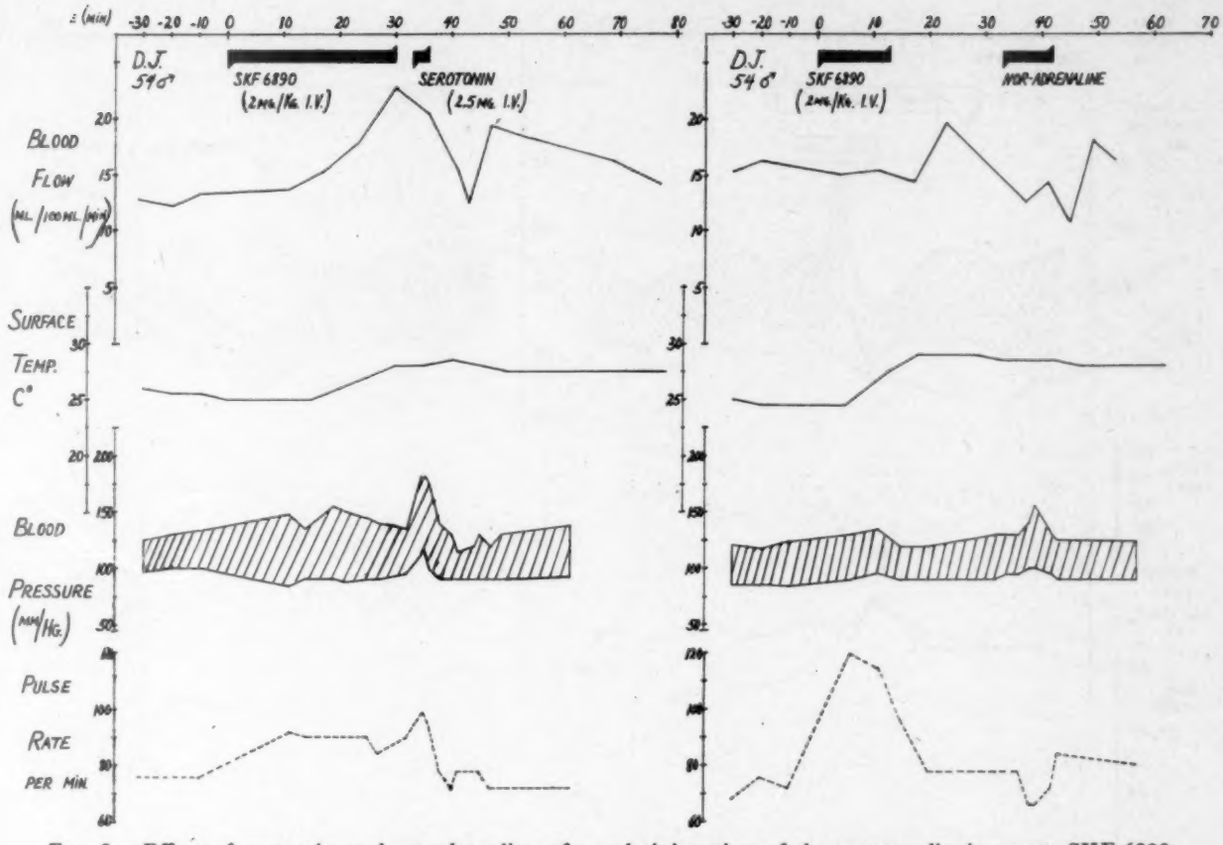

FIG. 2. Effect of serotonin and noradrenaline after administration of the postganglionic agent, SKF 6890.

awareness of the fact that some vascular beds serve specific physiologic functions[10–12] and may respond in their particular way independent of the simultaneously registered response in systemic arterial pressure.[13,14]

Based mainly on the marked pressor action of noradrenaline, there has been much speculation about a possible role of the catecholamines, in particular of noradrenaline, in the etiology of hypertension in human beings.[3,15,16] There exists a large body of indirect but highly suggestive evidence that the catecholamines are potent peripheral vasoconstrictors.[1–3]

Some of the observations made in our laboratory during the course of long term studies on vascular responses pertain to the action of catecholamines, especially noradrenaline. They have been abstracted and are reported here. For this reason, the methods and material used are indicated in the illustrations rather than discussed in a separate paragraph.

Study of the interaction of pressor and de-

TABLE I

Comparison of Some Actions of Noradrenaline and Serotonin in Man

Determination	No. of Experiments	Noradrenaline	Serotonin
Arterial pressure	12	Increase of systolic and diastolic pressure	Short-lasting increase of systolic and diastolic pressure with negative phase
Cardiac output	4	Moderate increase (30 to 50%)	Little change
Renal plasma flow p-amino hippuric acid (ml./minute)	7	Decrease (average 30%)	Increase (average 65%)
Extremity blood flow (ml./100 ml. tissue/minute)	7	Decrease	Transient small increase followed by longer lasting decrease

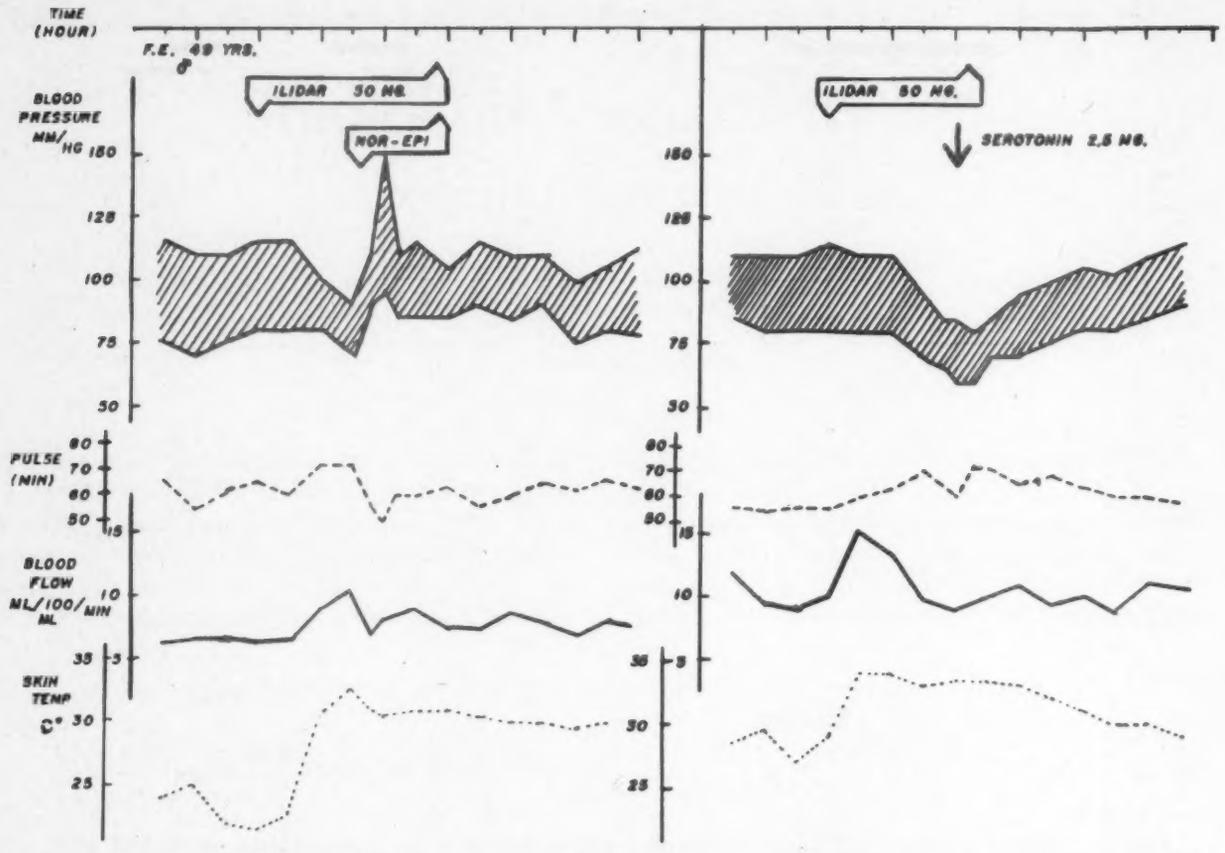

FIG. 3. Effects of administration of serotonin and noradrenaline in hypotension induced by administration of Ilidar.® Ilidar is a dibenamine-type adrenergic blocking agent.

pressor agents may be one of the many possible ways to attempt to arrive at a better understanding of some of the mechanisms involved in the regulation of systemic arterial pressure in man.

RESULTS

Circulatory Effects of Noradrenaline and Serotonin: We first compared two pressor substances, namely noradrenaline and serotonin. Noradrenaline was given by intravenous infusion, 4 mg. per 1,000 cc. at the rate of 20 drops per minute. It may be debatable whether serotonin should be called a pressor substance. However, with the dose of 2.5 mg. used we have almost invariably found that administration of serotonin produced a biphasic pressor response, namely, a short-lived increase followed by a likewise brief negative phase. Some effects of noradrenaline and serotonin administration on blood circulation in man are compared in Table 1.

Arterial pressure, extremity blood flow, cardiac output and renal plasma flow were studied. The two substances did not act alike in any of these measurements; they acted similar in the first two and different in the last two. The responses were directionally the same in normotensive subjects and in hypertensive patients, although the changes occurring in the various measurements were almost invariably more pronounced in hypertensive patients than in normotensive subjects.

Catecholamine Inhibitors: In a second set of experiments we compared the influence of pretreatment with four so-called "hypotensive" agents on the pressor action of noradrenaline and serotonin. These agents were a ganglionic blocking agent (Fig. 1), a postganglionic blocking agent (Fig. 2), an adrenergic blocking agent (dibenamine-type) (Fig. 3), reserpine (Fig. 4) and hydralazine (Fig. 5). The pressor action of noradrenaline was blocked only by administration of dibenamine-type agents. It remained effective during hypotension induced by administration of reserpine, hydralazine and ganglionic as well as postganglionic blocking agents.

In contrast, pressor action of serotonin was

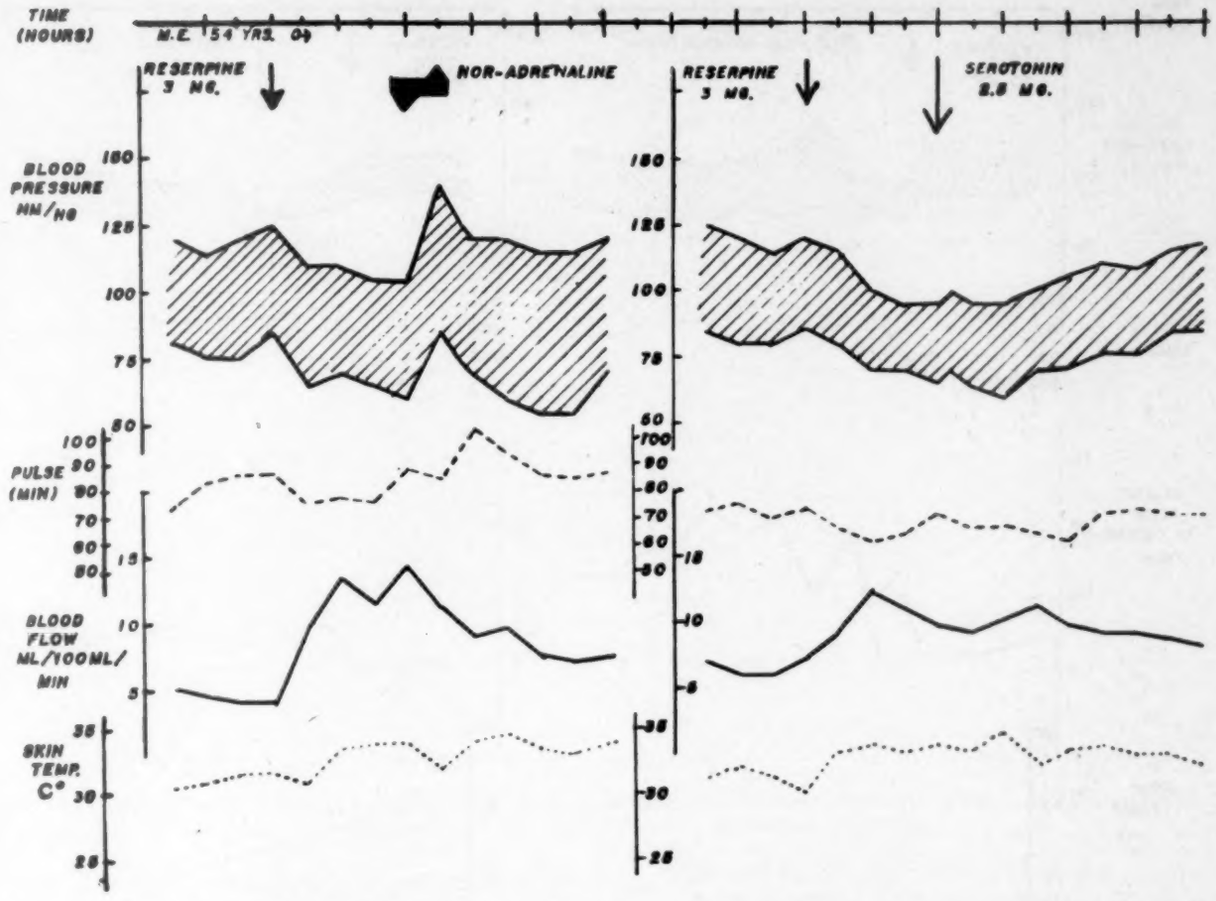

FIG. 4. Effects of administration of serotonin and noradrenaline in hypotension induced by administration of reserpine.

blocked by administration of agents other than ganglionic and postganglionic blocking agents. With the adrenergic blocking agent, the hypotensive effect was small; it was even smaller with the experimental drug SKF 6890, believed to be a postganglionic blocking agent. Both the adrenergic and the postganglionic blocking agents were originally investigated as hypotensive agents. In the course of the study, effects of their administration on peripheral blood flow were by far more impressive than their action on arterial pressure; both produced marked increase in peripheral blood flow (Fig. 6). Average responses to these two types of "catecholamine inhibitors" are also compared (Table II).

Catecholamine Potentiation: Next, we attempted to produce the opposite effect, namely potentiation of effects of catecholamines on extremity flow through interference with monoamine oxidase activity. There was regular and reproducible potentiation of action of noradrenaline after administration of JB 516 (Catron®), a

TABLE II

Comparison of Average Responses of Ten Patients with Occlusive Arterial Disease to Intravenous Administration of Two Catecholamine Inhibitors

Drug	Peripheral Blood Flow (%)	Surface Temperature (glomus area) (° C.)	Arterial Pressure (mm. Hg)	Duration of Response (min.)	Pulse Rate (per min.)
Azapetine	+82	+8	−15/10	74	0 to +10
SKF 6890	+101	+3.6	−15/10	64	0 to +10

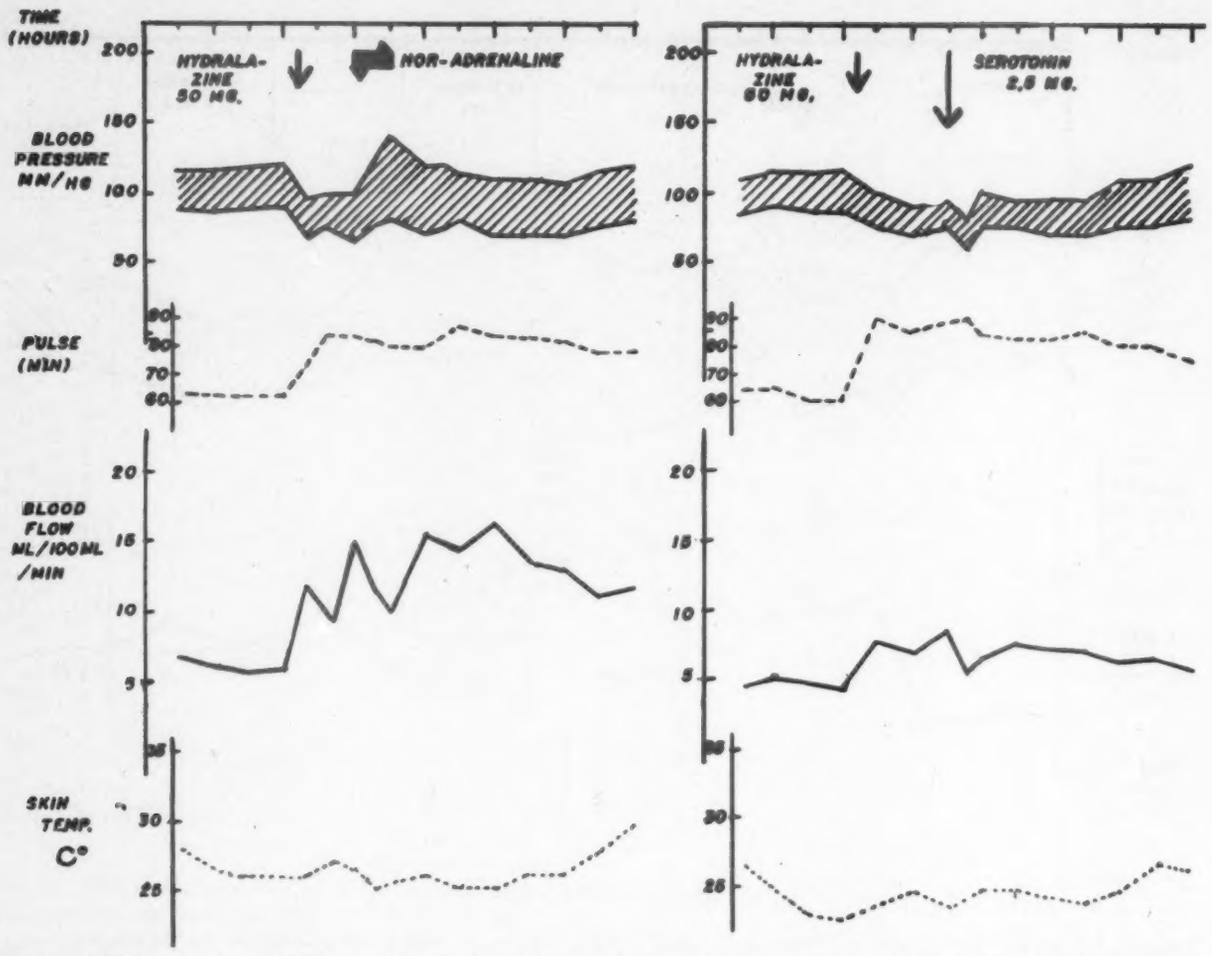

FIG. 5. Effects of administration of serotonin and noradrenaline in hypotension induced by administration of hydralazine.

potent monamine oxidase inhibitor (Fig. 7). This potentiation was questionable and irregular with adrenaline and was almost absent with serotonin.

SUMMARY

The effects of administration of noradrenaline and serotonin on systemic arterial pressure, cardiac output, renal plasma flow and blood flow to the lower extremities in man were compared. Modification of vascular responses to these two substances by drug-induced hypotension were studied. The results failed to support the hypothesis that noradrenaline may play a

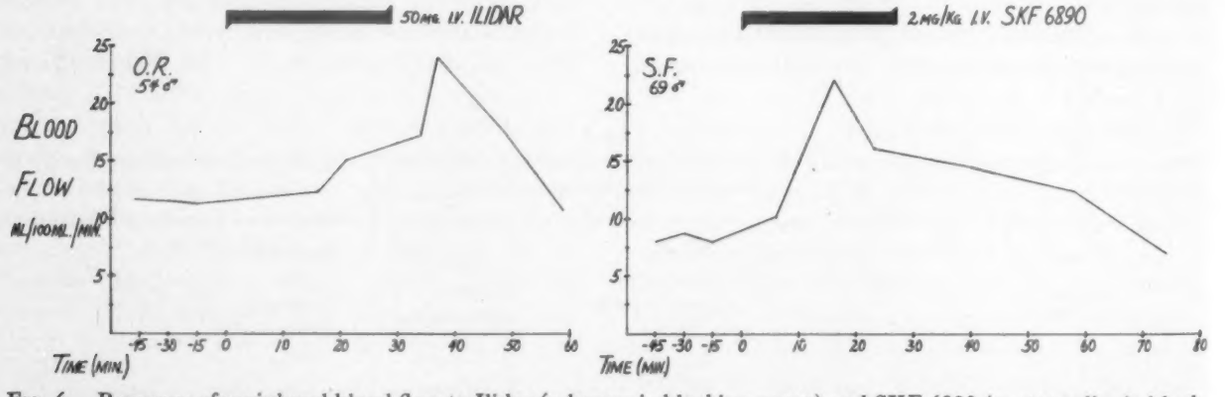

FIG. 6. Response of peripheral blood flow to Ilidar (adrenergic blocking agent) and SKF 6890 (postganglionic blocking agent).

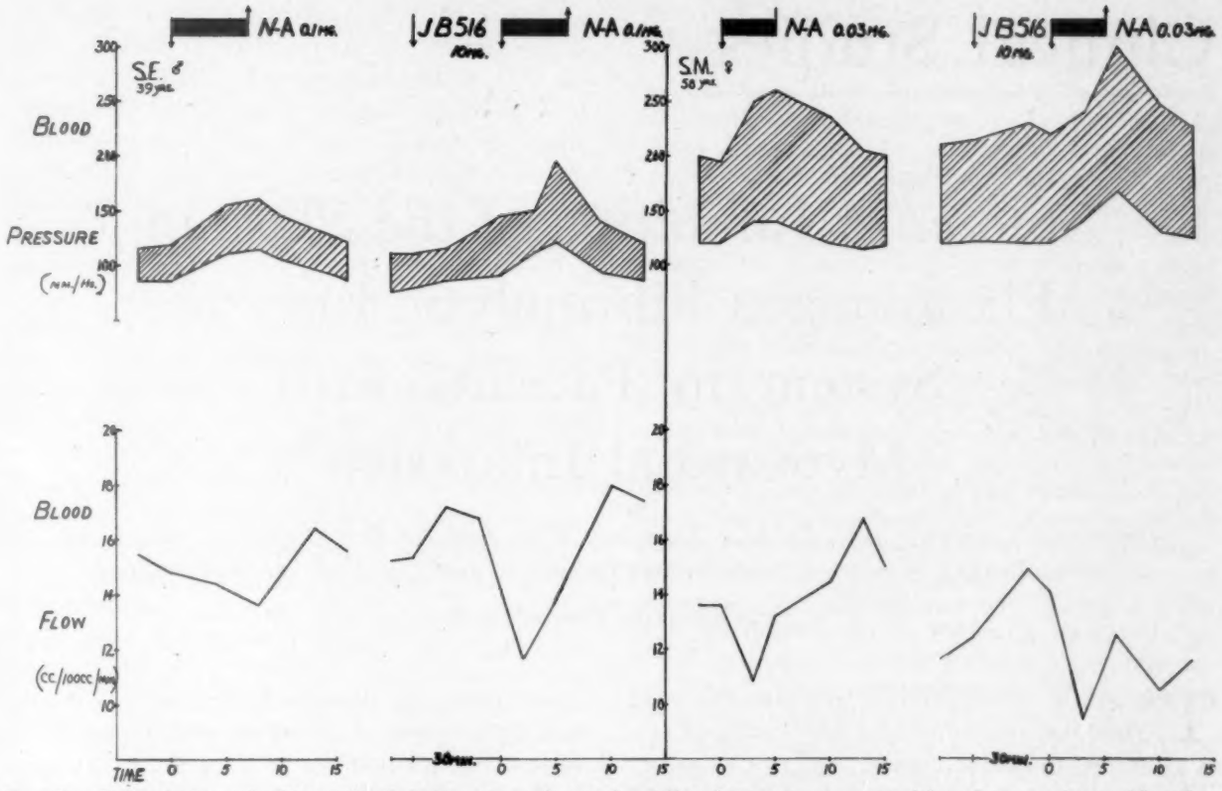

FIG. 7. Potentiation of effects of administration of noradrenaline by pretreatment with a monoamine oxidase inhibitor (JB 516) in normotensive subjects (*left*) and in patients with hypertension (*right*).

major role in the mechanism of hypertension in human beings. On the other hand, blood flow responses after administration of catecholamine inhibitors as well as after use of a monoamine oxidase inhibitor strongly support the view that noradrenaline is one of the most potent physiologic peripheral vasoconstrictors in man.

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Clinical Studies

Studies of Inhibition of the Plasmin-Plasminogen Fibrinolytic Enzyme System in Patients with Myocardial Infarction*

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THE PHASE of coagulation in which the fluid blood is transformed to a solid clot has been of interest to the clinician and physiologist. The development in recent years of highly purified proteolytic and fibrinolytic enzymes and their employment in the treatment of thromboembolic and inflammatory states[1–3] have aroused a similar interest in the converse process, fibrinolysis, or the dissolution of blood clots. Furthermore, it has been suggested by several workers[4–6] that impaired fibrinolytic mechanisms may underlie the pathogenesis of atherosclerosis. Recently, Hume[7] has described an apparent decrease in circulating fibrinolysin in patients with myocardial infarction during the first week of the disease. The further investigation of a possible mechanism for this decreased fibrinolytic activity forms the subject of this study.

Because of the recent interest in this subject, it might be appropriate to discuss briefly the various components of the fibrinolytic system.

THE FIBRINOLYTIC ENZYME SYSTEM OF HUMAN PLASMA

Although our knowledge of the fibrinolytic system in the human subject has many gaps, the scheme of Mullertz[8] represents the most widely held theory of plasmin activation. We will first define some of the terms used in describing fibrinolytic phenomena.

Plasmin (fibrinolysin) is the active proteolytic enzyme which is capable of digesting the fibrin matrix of clots and of hydrolyzing a number of proteins. It is present in minute amounts in normal blood and is completely neutralized by an inhibitor or inhibitors. *Plasminogen* is the inactive precursor of plasmin contained in the globulins of all known mammalian plasma. Certain activators of tissue, urine, blood and other sources, are capable of converting it to the active enzyme plasmin. *Plasminogenases* (plasminogen activators) are substances, present in tissue, urine and blood, capable of converting plasminogen into the active enzyme plasmin. *Lysoplastin* is a term for substances which can react with one or more components in blood to form an activator of plasminogen. *Antiplasminogenase* is an inhibitor of plasminogen activator present in the blood. *Antiplasmin* is an inhibitor of plasmin present in the plasma of all mammalian species. *Proplasminogenase* (proactivator of plasminogen) is a hypothetical substance which has never been completely isolated, but is believed to be present in large quantities in human plasma and in trace

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amounts in bovine plasma. The evidence for the existence of such a plasma proactivator is based on the fact that streptokinase readily activates the plasminogen of human plasma, but is unable to activate the plasminogen of bovine plasma.[9,10] If a small amount of human serum is added to streptokinase, however, a potent activator for all animal plasminogens is then obtained.

Under normal circumstances in fluid blood, all active substances circulate in a "neutralized" state and consequently do not split fibrinogen or plasma proteins. With clotting, however, plasminogen activator from the circulating blood is strongly adsorbed onto fibrin in the clot. It thus accumulates on the surface of fibrin deposits and can reach high local concentrations despite its low concentration in the blood itself. The activation of plasminogen takes place on the fibrin surface and the fibrin is subsequently digested by the plasmin found in the clot. By the lysis of fibrin, plasmin and plasminogen activators are released into the blood and neutralized by their respective inhibitors. A more detailed description of the biochemistry and mode of action of these substances may be found in several excellent reviews which have appeared in recent years.[4,8,11,12] The theory of Mullertz[8] is represented schematically by him in the following manner:

The Fibrinolytic Enzyme System of Human Plasma

Equilibria in fluid blood

Lysoplastin + plasminogen proactivator ⇄ plasminogen activator + inactive component

Plasminogen activator + antiplasminogenase ⇄ bound plasminogen activator

Plasmin + antiplasmin ⇄ bound plasmin

Equilibria and enzymatic reactions in presence of fibrin

Plasminogen activator is adsorbed from circulating blood onto fibrin

Plasminogen activator + fibrin ⇄ fibrin-plasminogenase (bound plasminogen activator) and hence:

Bound plasminogen activator ⇄ plasminogen activator + antiplasminogenase on the fibrin surface

Plasminogen $\xrightarrow{\text{plasminogenase}}$ plasmin

Fibrin $\xrightarrow{\text{plasmin}}$ protein fragments

It is a further possibility that fibrin also influences plasmin and antiplasmin in a similar way

Plasmin + fibrin ⇄ fibrin-plasmin and hence:

Bound plasmin ⇄ plasmin and antiplasmin

Material and Methods

Fifty-eight patients from the wards of the Philadelphia General Hospital, ranging in age from forty-five to seventy years, were utilized as the study group. All manifested the typical syndrome of recent myocardial infarction. The control group consisted of twenty-nine members of the resident staff and laboratory personnel of the Division of Cardiology of the Philadelphia General Hospital. Blood samples were drawn in iced syringes and delivered into balanced oxalate tubes surrounded by ice. The blood was immediately centrifuged and the plasma was separated from the cells. The plasma was frozen till the time of analysis.

The following studies were performed: (1) Plasma fibrinogen was determined by the quantitative method outlined by Stefanini and Dameshek.[13] (2) Lysis time of a standard bovine clot by undiluted plasma and plasma diluted 1:20 in imidazole-saline-buffer (ISB)[14] was also determined. The clot was prepared in the following manner: 0.2 ml. of 1 per cent bovine fibrinogen in ISB made up to pH 7.4, 0.2 ml. of human thrombin (Fibrindex®) 4 units/cc. and 0.4 ml. of plasma or plasmin-containing medium. Fresh reagents were prepared on the day of analysis. The tubes were placed in a water bath at 37°C. and the lysis time determined by inverting the tubes at regular intervals until the clot failed to cling to the bottom of the tube. The time of mixing rather than that of actual clot formation was used as zero time. A standard curve was constructed using serial dilutions of thrombolysin in ISB as the plasmin containing medium (lots No. 1125 and 1290), plotting lysis time against concentration of thrombolysin on log-log paper.

Test for Plasmin Inhibitor: Utilizing thrombolysin from the same lot in dilutions of 2,000 Merck units/cc., 0.4 ml. of 1:10, 1:20 and 1:40 dilutions of thrombolysin in ISB were added to the fibrinogen-plasma-thrombin mixture described and the lysis times of the clot incubated with each of these plasmin dilutions were determined. Another curve was constructed in which the lysis times of clots formed with fibrinogen concentrations from 300 to 1,000 mg./100 ml. were determined when incubated with each of the aforementioned plasmin dilutions. This was carried out to determine the effect of an increased fibrinogen blood level on the lysis time independent of the inhibitor.

Results

Normal Control Subjects: Table 1 shows the lysis time of the various plasmin* dilutions in ISB when they were incubated with plasma of

* Thrombolysin contains considerable activator activity as well as fibrinolytic activity. No distinction has been made between inhibition to plasmin and plasminogen activators in these studies.

TABLE I
Antiplasmin Lysis Times in Twenty-Nine Normal Control Subjects

Case No.	Antiplasmin Lysis Time (sec.)			Plasma Lysis Time (sec.)	
	Plasmin Diluted 1:10 in ISB	Plasmin Diluted 1:20 in ISB	Plasmin Diluted 1:40 in ISB	Undiluted Plasma	Plasma Diluted 1:20 in ISB
1	267	533	751	1200+	1200+
2	248	500	847	1200+	1200+
3	227	544	852	1200+	1200+
4	206	510	880	1200+	1200+
5	185	499	855	1200+	1200+
6	168	470	860	1200+	1200+
7	221	476	856	1200+	1200+
8	234	479	667	1200+	1200+
9	258	837	538	1200+	1200+
10	197	592	573	1200+	1200+
11	198	277	364	1200+	1200+
12	202	399	607	1200+	1200+
13	211	363	451	1200+	1200+
14	271	525	998	1200+	1200+
15	186	318	674	1200+	1200+
16	206	393	963	1200+	1200+
17	220	646	1200+	1200+	1200+
18	181	620	1008	1200+	1200+
19	169	364	610	1200+	1200+
20	244	453	593	1200+	1200+
21	194	294	574	1200+	1200+
22	175	330	584	1200+	1200+
23	297	549	617	1200+	1200+
24	197	454	708	1200+	1200+
25	154	507	QNS	1200+	1200+
26	339	662	1028	1200+	1200+
27	136	431	859	1200+	1200+
28	117	552	872	1200+	1200+
29	QNS	422	755	1200+	1200+
Mean	211 ± 47	468 ± 146	755 ± 191	1200+	1200+

NOTE: QNS = quantity not sufficient.

normal control subjects. The average lysis time of the 1:10 dilutions of plasmin was 211 ± 47 seconds, of the 1:20 dilutions 468 ± 146 seconds and of the 1:40 dilutions 755 ± 191 seconds. No spontaneous lytic activity was shown by the undiluted or 1:20 dilutions of plasma in ISB.

Patients with Myocardial Infarction: Table IIA shows the lysis times of the various plasmin dilutions in ISB when they were incubated with plasma of patients with acute myocardial infarction who were treated with heparin. Thirty-seven blood samples were tested. It can be readily observed that the lysis times of all dilutions of plasmin in ISB are much longer than those incubated with plasma of the control group.

Table IIB shows similar data for the plasma of patients with acute myocardial infarction who were not treated with heparin. There is no statistically significant difference between the two groups of patients with myocardial infarction. Both show much longer lysis times than the control group when incubated with the various dilutions of plasmin. Although the patients with myocardial infarction are considerably older than those of the control group, data accumulated in our laboratory have failed to demonstrate that age, *per se*, is an important factor in the increased inhibition to plasmin activity.

Fibrinogen Levels: Table III shows the plasma fibrinogen levels of the respective groups. The fibrinogen levels are higher in the patients with

myocardial infarction than in the control subjects.

Table IV shows the effect of increased fibrinogen on the time required to lyse a standard clot by various dilutions of plasmin. While increased fibrinogen in high concentrations slightly prolongs the clot lysis time, the prolongation does not reach the order of magnitude shown in our data for plasma inhibitors (Tables I and II).

Comments

Evidence for Increased Inhibitor of Plasmin-Plasminogen System in Episodes of Myocardial Infarction: From the data presented in Tables I and II it can be readily observed that fixed concentrations of plasmin require longer times to dissolve standard fibrin clots when they are incubated with the plasma of patients with acute

Table II

Antiplasmin Lysis Time in Patients with Acute Myocardial Infarction

Case No.	Antiplasmin Lysis Time (sec.)			Plasma Lysis Time (sec.)	
	Plasmin Diluted 1:10 in ISB	Plasmin Diluted 1:20 in ISB	Plasmin Diluted 1:40 in ISB	Undiluted Plasma	Plasma Diluted 1:20 in ISB
	A. Patients Treated with Heparin				
1	420	1169	1200+	1200+	1200+
2	569	1200+	1200+	1200+	1200+
3	305	649	1200+	1200+	1200+
4	224	393	1013	1200+	1200+
5	No clot	No clot	No clot	No clot	No clot
6	199	315	560	1200+	1200+
7	405	907	1200+	1200+	1200+
8	395	879	1200+	1200+	1200+
9	206	444	1002	1200+	1200+
10	No clot	No clot	No clot	No clot	No clot
11	Incomplete clot	Incomplete clot	Incomplete clot	Incomplete clot	Incomplete clot
12	Incomplete clot	Incomplete clot	Incomplete clot	Incomplete clot	Incomplete clot
13	256	436	1018	1200+	1200+
14	283	991	1200+	1200+	1200+
15	413	1200+	1200+	1200+	1200+
16	471	1200+	1200+	1200+	1200+
17	259	736	1200+	1200+	1200+
18	389	1200+	1200+	1200+	1200+
19	482	1017	1200+	1200+	1200+
20	194	706	1200+	1200+	1200+
21	233	325	697	1200+	1200+
22	508	931	1200+	1200+	1200+
23	232	365	449	1200+	1200+
24	318	1211	1200+	1200+	1200+
25	366	1200+	1200+	1200+	1200+
26	305	1200+	1200+	1200+	1200+
27	281	1202	1200+	1200+	1200+
28	No clot	No clot	No clot	No clot	No clot
29	220	508	1054	1200+	1200+
30	258	361	1200+	1200+	1200+
31	394	1200+	1200+	1200+	1200+
32	133	312	704	1200+	1200+
33	263	545	1012	1200+	1200+
34	306	457	1010	1200+	1200+
35	305	649	1200+	1200+	1200+
36	405	907	1200+	1200+	1200+
37	224	393	1013	1200+	1200+

Continued on following page

TABLE II—*Continued*
Antiplasmin Lysis Time in Patients with Acute Myocardial Infarction

Case No.	Antiplasmin Lysis Time (sec.)			Plasma Lysis Time (sec.)	
	Plasmin Diluted 1:10 in ISB	Plasmin Diluted 1:20 in ISB	Plasmin Diluted 1:40 in ISB	Undiluted Plasma	Plasma Diluted 1:20 in ISB
			B. Untreated Patients		
38	651	1200+	1200+	1200+	1200+
39	424	1076	1200+	1200+	1200+
40	502	1190	1200+	1200+	1200+
41	194	670	1169	1200+	1200+
42	175	713	783	1200+	1200+
43	287	568	1200+	1200+	1200+
44	269	490	1050	1200+	1200+
45	256	374	810	1200+	1200+
46	659	1200+	1200+	1200+	1200+
47	436	666	789	1200+	1200+
48	456	1200+	1200+	1200+	1200+
49	482	1200+	1200+	1200+	1200+
50	404	1200+	1200+	1200+	1200+
51	398	1200+	1200+	1200+	1200+
52	249	361	1200+	1200+	1200+
53	239	606	1200+	1200+	1200+
54	286	590	1200+	1200+	1200+
55	1200+	1200+	1200+	1200+	1200+
56	317	515	1014	1200+	1200+
57	423	1200+	1200+	1200+	1200+
58	239	385	866	1200+	1200+

myocardial infarction than with the plasma of normal control subjects. The data presented in Tables III and IV demonstrate that this prolongation in clot lysis time cannot be solely attributed to the increased plasma fibrinogen concentration found in these patients. Since it is well known[15] that the ability of a plasmin solution to dissolve standard fibrin clots is markedly diminished if this plasmin mixture is incubated with the plasma of all mammalian species studied to date, we are therefore led to the conclusion that a greater amount of this inhibitor substance is present in the plasma of patients with acute myocardial infarction than is found in normal control subjects. The decrease in circulating fibrinolysin described by Hume[7] in such persons may in reality be a manifestation of such increased inhibitor activity to the plasmin-plasminogen system.

Nature of Plasmin-Plasminogen Inhibitors in Man: It has been known for more than a half-century that normal serum possesses factors which inhibit the action of proteolytic enzymes,[15,16] but controversy still surrounds the nature and number of components capable of inhibiting plasmin and plasminogen activators. Christensen and MacLeod[17] demonstrated that inhibitory activity against serum proteinase resides in the albumin fraction of serum subjected to ammonium sulfate precipitation. Using the Cohn fractionation method,[18] Grob[19] found that protein fractions IV-1 and IV-4 had the greatest inhibitory activity per unit nitrogen against serum proteinase, but since these represented only 5 and 5.8 per cent of the plasma proteins, the albumin fraction (fraction V) contributes a greater overall effect to the plasma inhibitors of proteolytic enzymes. When he reconstituted plasma protein fractions of the same concentration as those found in plasma, the sum of the inhibition was less than 25 per cent of that obtained by the plasma as a whole. Grob therefore postulated that non-protein components, such as polypeptides described by Northrop[20,21] against trypsin, might also contain serum proteinase inhibitors.

In 1948 Ratnoff[22] postulated that there may be several plasma inhibitors and in 1954[23] believed that he had demonstrated three such inhibitors: (1) heat labile, destroyed by heating at 56° C. for thirty minutes; (2) a heat stable

TABLE III
Plasma Fibrinogen Levels in Normal Control Subjects and Patients with Acute Myocardial Infarction

Plasma Fibrinogen Concentration (mg. %)		
Normal Control Group*	Patients with Acute Myocardial Infarction	
	Not Treated with Heparin†	Treated with Heparin‡
300	610	620
347	621	335
305	460	792
273	460	738
300	567	524
305	418	556
305	519	562
347	535	272
310	735	433
262	439	508
308	353	275
	378	539
		418
		457
		620
		867
		556
		535
		326
		900

* Mean: 305.6 ± 19.1. † Mean: 507.9 ± 106.6. ‡ Mean: 541.7 ± 175.5.

component, which was inactivated by ammonia and primary amines; and (3) a component stable to both heat and chemicals. Norman[24,25] found but two inhibitors. Using a caseinolytic assay, he found that one was a rapidly acting component more stable at extremes of heat and pH than the other component. The immediate (or rapidly acting) inhibitor migrates as an alpha-2 globulin during starch electrophoresis. The slow component migrates as an alpha-1 globulin and is readily destroyed by heat. He feels that the inhibitor of plasmin described by Shulman in 1952[26] was probably his heat stable immediate reactor. Norman also believes that the third component described by Ratnoff is probably an artefact. The apparent inhibitor destroyed by primary amines was actually autodigestion of plasmin. This process was prevented by the stabilizing effect on plasmin of the primary amines.

Shulman[27] recently isolated an inhibitor from urine and plasma of molecular weight of approximately 16,700. It accounts for only about 3 per cent of the inhibitor activity in the plasma.

TABLE IV
The Effect of Increased Fibrinogen Concentration on the Lysis Time of the Plasma Dilutions

Concentration of Fibrinogen Solution (mg./ml.)	Lysis Time (sec.)		
	Plasmin Diluted 1:10 in ISB	Plasmin Dilution 1:20 in ISB	Plasmin Dilution 1:40 in ISB
11	Incomplete clot	107	118
12	Incomplete clot	104	126
13	Incomplete clot	100	131
14	Incomplete clot	100	136
15	Incomplete clot	102	138
16	Incomplete clot	110	128
17	Incomplete clot	104	132
18	Incomplete clot	106	134
19	Incomplete clot	111	133
20	Incomplete clot	117	137

NOTE: Contents of incubation mixtures: 0.2 ml. fibrinogen solution; 0.2 ml. human thrombin (4 units/ml.); 0.4 ml. plasmin (thrombolysin lots No. 1125 and 1290) diluted in ISB, 2,000 Merck units/ml.

He felt that it might be similar to the inhibitor isolated from bovine plasma by Schmitz.[28] It is interesting to speculate on the relationship between this polypeptide and that recently described by Unger and Adler[29] which is capable of hydrolyzing glycyl beta naphthylamine and has properties similar to antifibrinolysin.

Mullertz[9] thought that he found strong evidence for an inhibitor of the activator of plasminogen when he discovered that crude bovine globulin inhibited the activation of bovine plasminogen by human streptokinase-activated globulin. This inhibition was markedly reduced in the presence of fibrin. Norman,[24] using a caseinolytic assay, found that normal serum contains about thirty times as much antiplasmin as plasminogen capable of being converted into plasmin. Sherry[11] feels the ratio is much smaller.

Plasmin-Plasminogen Inhibitors in Disease States: Even more controversy is found when the changes of inhibitors in disease states are discussed. Guest and co-workers[30] state there is increased antifibrinolysin in patients with pneumonia, intestinal obstruction, cirrhosis of the liver, coronary thrombosis, acute bacterial endocarditis and acute streptococcal infections. In Grob's review of the earlier literature,[31] he observed that antiproteolytic activity of the serum increased markedly in the presence of malignant tumors, anaphylaxis, protein shock

therapy, pregnancy, severe exercise and also postprandially. He also reported increased antitryptic activity following oral ingestion of trypsin. Shulman[32] concurred in the increase in antitryptic activity in most cases of tissue necrosis and found that the increased activity closely followed sedimentation rates (when not due to abnormal globulin) and the blood fibrinogen levels. On the other hand, he found that very few of these conditions demonstrated antiplasmin activity by his criteria.

Our data do little to settle this controversy. There is unequivocal prolongation of the lysis time when plasmin is added to these pathologic blood sera in our study, but whether this is due to an inhibitor of plasminogen activator or due to an antiplasmin is not determined. The decreased plasmin activity reported by Hume[7] in patients with myocardial infarction may actually be evidence of increased plasmin inhibitor activity noted in our study. The increased antiplasmin activity found in our series appears to be further confirmation of the considerable body of evidence pointing toward impaired fibrinolytic processes as an important factor in the development of atherosclerosis.

Inhibitory agents have been found in various tissues.[33] Albumin fractions of the extracts of various organs show highest activity in the spleen and liver.[34] Astrup[35] has recently presented data that fibrinolytic activity is least in the intima of the blood vessels and becomes progressively greater as it extends toward the adventitia. Kwaan[36–38] has suggested that vasoconstriction of the vasa vasorum, by producing ischemia of the wall of the vein, is a common mechanism underlying the production of fibrinolytic activity in veins. The ischemia results in stimulation of the effector mechanism, followed by release of activator into the circulation. He has recently presented evidence for a similar mechanism in the arterial wall which may be inhibited by exercise.

Summary

The plasma of twenty-one patients with acute myocardial infarction who had not received heparin and the plasma of thirty-seven patients with acute myocardial infarction who had received heparin were tested for antiplasmin activity. The plasma of twenty-nine control subjects was similarly tested. Plasma fibrinogen levels were determined in these groups. Antiplasmin activity was increased significantly over the control group in both groups of patients with myocardialin farction. Plasma fibrinogen levels paralleled the increased antiplasmin activity.

A brief review of the literature on fibrinolysin inhibitors and their possible relation to the pathogenesis of atherosclerosis is discussed. The increased antiplasmin activity in patients with myocardial infarction appears to confirm the importance of impaired fibrinolytic processes in atherosclerosis.

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The Fibrinolytic System and Use of Fibrinolysin in Myocardial Infarction

Preliminary Report*

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As early as 1893, the spontaneous lysis of blood clots was observed and explained by Dastre[1] on the basis of a proteolytic enzyme in serum. In 1906, Morawitz[2] also demonstrated fibrinogenolytic and fibrinolytic properties of postmortal blood. Clinically, clot lysis has been reported in acute febrile infections,[3] in shock,[4] after traumatic injuries or burns[5] or even in normal persons who have performed heavy physical exercise.[6] In 1946, Tagnon and co-workers[7] observed increased fibrinolytic activity in the blood of patients suffering from severe burns and hemorrhagic diathesis. Similar observations have been made with regard to hemorrhagic conditions observed in obstetric cases, fetal death *in utero* and amniotic fluid infusion.[2,8] Plasmin attacks the formation of thrombi directly and may actually supplement the effects of anticoagulant therapy. Although considerable experimental and clinical data are available relative to the use of plasmin in thromboembolic disease at various sites, especially peripheral phlebothrombosis and thrombophlebitis, there are comparatively little data relative to its use in the treatment of coronary arterial occlusion.

In recent years many preparations have been used in an attempt to dissolve intravascular clots. The proteolytic enzymes[9–19] trypsin, chymotrypsin and streptokinase have been investigated both clinically and in the experimental animal, in efforts to produce lysis of thrombi. Although trypsin and chymotrypsin have been effective in causing resorption of edema and reversing inflammation, they have been ineffective in dissolving thrombi.[10–13] Moreover, pyrogenic and hypotensive reactions frequently attended their systemic use.

Another approach, using streptokinase to rapidly activate the rate of change of plasminogen to plasmin, has been studied.[14–19] Early attempts to use partially purified streptokinase systemically were successful in dissolving pleural exudates and liquefying thrombi. Unfortunately, these preparations were highly antigenic and were accompanied by pyrogenic and hypotensive reactions. Using a highly purified streptokinase, Sherry and his co-workers[18,19] have shown, in recent studies, a marked diminution of such reactions. The increased antithrombin activity, the decreased Ac globulin and prolongation of the prothrombin time caused by this infusion, however, have produced a state of hypocoagulability in some patients. In these patients blood tended to ooze from venous puncture sites and ecchymoses were later found at other injection sites. This area of investigation is promising, however, and merits further clinical trials.

A third approach, utilizing the fibrinolytic enzyme plasmin to dissolve the thrombus and restore blood flow through the occluded vessel, was employed in the present study. Earlier preparations of plasmin also resulted in pyrogenic and hypotensive reactions[20,21] which became less severe with the development of more highly purified preparations.

The object of this study is to report our experience with the use of plasmin in cases of acute

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coronary occlusion and to document the possible mechanism of its effect.

Material and Methods

Twenty-eight normal adults were studied for the presence of plasmin and antiplasmin activity. The twenty minute clot lysis method by undiluted plasma and plasma diluted 1:20 in imidazole-saline buffer (ISB) was used for determining plasmin activity.[22] Antiplasmin activity was determined by the prolongation of the time required for various concentrations of thrombolysin* to dissolve a standard bovine fibrin clot, when incubated with the undiluted plasma of the patient.[23] Similarly, plasmin and antiplasmin activity were determined in thirty patients with acute myocardial infarction. Seventeen of the thirty patients had not received heparin, while thirteen had been treated with heparin. Blood samples were drawn on admission and daily for three to four days thereafter.

Patients with a clinical history, electrocardiographic changes and physical findings suggestive of acute myocardial infarction were the subjects in this study. An attempt was made to use patients whose infarction was seventy-two hours or less in duration, dating the onset of infarction from the first episode of severe, intractable, precordial and substernal pain. Control vital signs, electrocardiogram, serum glutamic oxalacetic transaminase (SGOT), white blood cell count, hemoglobin, clotting time (Lee-White), prothrombin time, plasma fibrinogen and plasmin activity were obtained. These studies were then repeated serially after plasmin infusion. During the period of plasmin administration, the blood pressure, pulse rate, respiration rate and temperature were recorded every thirty minutes.

The usual regimen employed in the treatment of myocardial infarction was otherwise unchanged. All patients were given anticoagulants such as heparin and dicumarol. Benadryl,® 50 mg., was administered to two patients prior to the plasmin infusion in an attempt to minimize or prevent the pyrogenic reaction often observed with early preparations then in use.

Electrocardiograms, SGOT, plasmin activity and fibrinogen levels were obtained routinely before and after plasmin infusion. Blood for determination of plasmin activity was carefully drawn and spun down in centrifuged tubes packed with ice. The plasma was then removed and frozen till the time of analysis. Plasmin activity was determined spectrophotometrically using benzoyl arginine methyl ester (BAME) as the substrate, the activity being expressed in BAME units.[24]

The plasmin† was administered intravenously in 500 cc. of 5 per cent dextrose in water over an average period of two to four hours. One hundred thousand units were used as the initial dose in six patients (Cases 1 to 6). In Case 7 the initial dose was 200,000 units, tapered off to 100,000, 75,000 and 50,000 units on the succeeding days. One patient (Case 8) received 200,000 units of thrombolysin initially, followed by 150,000 and 100,000 units, respectively, on the two succeeding days.

Results

Antiplasmin Lysis Times: The twenty minute clot lysis time determinations on the twenty-eight normal subjects and thirty patients with acute myocardial infarction failed to show significant levels of plasmin activity. Antiplasmin determinations in the group of normal subjects showed an average clot lysis time of 211 ± 47 seconds against 80 Merck units of plasmin, 468 ± 146 seconds against 40 units of plasmin and 755 ± 191 seconds against 20 units of thrombolysin. The seventeen patients with acute myocardial infarction who had not received heparin showed an average clot lysis time of 440 seconds against 80 plasmin units, 857 plus seconds (with seven patients showing a lysis time of greater than 1,200 seconds) against 40 plasmin units and 1,095 plus seconds (with eleven patients showing a lysis time of greater than 1,200 seconds) against 20 plasmin units. A more detailed analysis of these data has been presented in a previous report.[23]

Effects of Plasmin Therapy: A total of ten patients with the clinical diagnosis of acute myocardial infarction were treated with plasmin (Table 1). Following the infusion, three of the patients had a temperature of 103°F. and two a temperature rise of 1°F. with the remaining five manifesting no febrile reaction. Chills and chilly sensations were noted in those patients with high fever and were usually associated with a mild, transient hypotension, accompanied by flushing (Fig. 1). Because of the short duration of the hypotension, a vasopressor drug was not required. The chills and chilly sensations were controlled with 20 to 50 mg. of Benadryl administered intravenously and the pyrexia was usually limited to a period of six to eight hours. In one patient vomiting occurred (Case 7). In five patients, electrocardiographic changes in the form of improvement of S-T segment and T wave changes of

* Human fibrinolysin, Merck Sharp & Dohme. Thrombolysin contains considerable activator activity as well as fibrinolytic activity. No attempt has been made to differentiate between inhibition to plasmin and plasminogen activators in this study.

† Actase® Fibrinolysin (Human), Ortho Pharmaceutical Corporation.

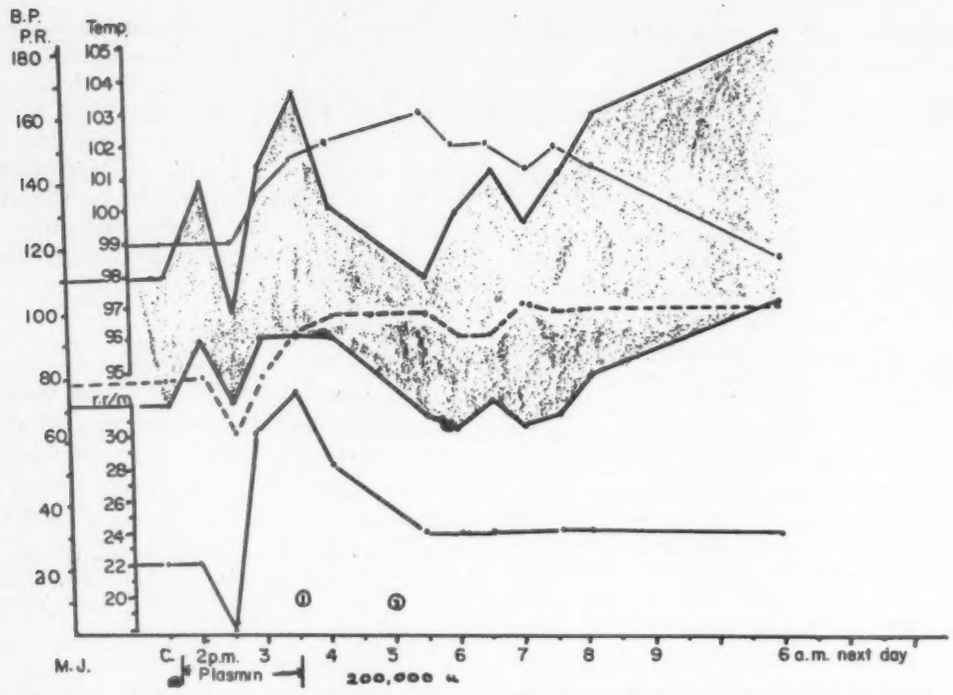

FIG. 1. Case 7. Effects of plasmin infusion on temperature, pulse, respiration and blood pressure in a typical patient. The top line shows the changes in rectal temperatures obtained before, during and the subsequent twenty-four hours after a single dose (200,000 units) of plasmin. The shaded area represents the changes in pulse pressure, the limits of which are defined by the systolic and diastolic pressures. The broken line represents the changes in pulse rate, and the lowest line represents changes in the respiratory rate. The graph shows that during administration of plasmin there was a progressive rise in the rectal temperature, a transient fall in blood pressure, pulse rate and respiratory rate which subsequently rose to levels above the control. ① = substernal pressure. ② = vomited twice.

ischemia were observed immediately following the infusion and could probably be attributable to the plasmin infusion. These electrocardiographic changes of infarction tended to recur when the thrombolysin effects disappeared. In the five other patients there were no alterations in the electrocardiogram which could be attributed to the plasmin infusion.

Eight of the ten patients were relieved of precordial or substernal pain. In all these patients no subsequent narcotics were required. Laboratory studies showed essentially no change in the blood fibrinogen levels with doses of 100,000 units. There was no difficulty encountered from administration of anticoagulants to these patients and in no instance was there any hemorrhagic manifestation.

Fibrinolytic activity of the blood of these patients before plasmin administration varied from 0 to 13 BAME units which was increased to 14 to 35 BAME units after plasmin infusion. The increased plasmin activity lasted for only forty-eight to seventy-two hours after the plasmin infusion.

COMMENTS

Although numerous gaps still exist in our knowledge of the mechanisms activating and inhibiting fibrinolysis *in vivo*, the following mechanisms are accepted by most investigators. Circulating plasminogen (an inactive precursor of plasmin) is activated into plasmin (active proteolytic and fibrinolytic enzyme) by various substances called activators, which are of tissue, humoral or bacterial origin.[2] The active plasmin then acts on both fibrin and fibrinogen, breaking them down into simpler protein molecules. The lesser fibrinolytic effect on the latter has been ascribed to the prevention of access of the active enzyme to the fibrinogen molecule, by the presence of circulating plasmin inhibitors (antiplasmins).[2] In our series of patients with acute myocardial infarction, no detectable plasmin activity was noted in the twenty minute clot lysis time immediately after the episode of myocardial infarction. These observations agree with the results reported by Hume.[25] The significantly higher antiplasmin levels in the patients with myocardial infarction

TABLE 1

Effects of Plasmin Therapy in Patients with Acute Myocardial Infarction*

Case	Age and Sex	Duration of Symptoms Before Infusion (hr.)	Total Plasmin Dose (units)	Electrocardiographic Changes after Plasmin Infusion	Untoward Effects	Clinical Observations
1	50, M	72	100,000	None	Temperature of 103° F.; headache; chills; flushing	Relief of pain in the chest; uneventful clinical recovery
2	61, M	48	100,000	Decreased T wave inversion in precordial leads	Chilly; rise in temperature of 1 °F.	Complete relief from pain in the chest
3	74, M	48	100,000	None	None	No recurrence of pain postplasmin
4	64, M	48	100,000	None	None	Patient in irreversible shock at the time of infusion; condition not altered; died 24 hours later
5	44, M	48	100,000	None	Rise in temperature of 1 °F.	Relief of pain in the chest; clinical recovery uneventful
6	56, F	24	100,000	None	Temperature of 103 °F.; mild hypotension; flushing	No change; no relief of pain in the chest
7	48, F	3	200,000 100,000 75,000 50,000 (on 4 successive days)	Marked improvement in ST-T wave changes of acute anterolateral myocardial infarction immediately after infusion	Temperature of 103° F.; mild hypotension; nausea; vomiting; flushing on first day; slight pyrexia with succeeding infusions	Relief of pain in the chest; SGOT 10 units on administration; rose to 35, 48 hours later; then returned to 10 units reproducible for 4 succeeding days
8	48, M	12	200,000 150,000 100,000 (on 3 successive days)	Marked T wave improvement; decrease in S-T segment elevation after infusion	None	Marked relief of pain in the chest; SGOT rise to 45 units only; uneventful clinical recovery
9	40, M	72	200,000 200,000 (at 12 hour intervals)	Arrest in development of deep, inverted T waves	None	Complete relief of angina
10	61, F	4	200,000 200,000 200,000 200,000 200,000 200,000 (on 3 successive days)	Deep T wave inversions failed to develop for 4 weeks after therapy with plasmin	None	Significant relief of pain within a few hours

* The first seven cases received Actase Fibrinolysin (Human). The remaining three received thrombolysin.

as compared with the normal control subjects, however, suggest that there may have been an increase in plasmin activity, which might have been masked by the simultaneous development of significantly higher antiplasmin activity. An interesting possibility is that the elevated antiplasmin titer in these conditions preceded and precipitated the development of the acute episode instead of being an aftermath of the occlusive state.

In myocardial infarction, therefore, the problem of lysing the clot is made more difficult because of the presence of a high antiplasmin titer. It is possible that this unfavorable shift of the

coagulation-fibrinolysis balance from fibrinolytic activity to the coagulating mechanism may explain the absence of spontaneous lysis and restoration of blood flow through the affected coronary artery after myocardial infarction. Thus, the parenteral administration of more plasmin seems to be a logical approach to the treatment of this condition.

The efficacy of plasmin in dissolving clots in the peripheral veins and the coronary and pulmonary arteries has been extensively demonstrated in experimental animals by various investigators,[26–31] using radiopaque clots or I^{131} tagged fibrinogen. *In vitro*, clot lysis has been demonstrated to take place in the presence of fibrinolysin.[32] Recently, Nydick and co-workers[33] produced infarction experimentally in dogs and administered plasmin one to fourteen days later. They found that in the untreated animals large confluent infarctions developed. Microscopic sections showed the capillaries and smaller vessels to be occluded with fibrinous material (microthrombi). In the animals treated with plasmin, the smaller vessels and capillaries were free of such occlusions and the infarctions observed were small and scattered. In view of the encouraging results obtained in the laboratory and in experimental animals, the use of plasmin has been extended to man. Ambrus,[20] in a report of nineteen cases, noted chills, increased basal metabolic rate, pyrexia and occasional hypotension. Cliffton,[21] who reported on forty patients, noted similar reactions in about 50 per cent. In the first seven patients with myocardial infarction which we treated with plasmin (Table 1), similar untoward effects were noted. All have been of a transient nature. No such reactions were noted in the last three patients. In our limited series, no significant changes were noted in fibrinogen blood levels following plasmin therapy, or have there been any hemorrhagic complications.

There is difficulty in determining an optimum schedule of plasmin therapy because of the following factors: (1) varying degrees of antiplasmin (inhibitor) levels in the patients prior to therapy; and (2) variability in the antiplasmin response of the patients to a fixed dose of plasmin. Therapeutic effects have been observed with an initial dose of 100,000 Merck units of plasmin. Increasing benefit has been observed in more recent experience with larger doses repeated at intervals of twenty-four to thirty-six hours. Experience has also pointed out the necessity of beginning fibrinolysin therapy within forty-eight hours of the infarction and of continuing administration of the drug for several days. It is interesting to note that similar non-uniformity of response to therapy was reported in the treatment of thrombo-occlusive diseases with highly purified streptokinase. Since the low antiplasmin levels failed to neutralize the circulating plasmin thus produced, ecchymoses and hypocoagulability of the blood occurred in isolated cases of these studies.[18,19]

Summary

Twenty-eight normal subjects and thirty patients with acute myocardial infarction were studied for spontaneous fibrinolytic activity and antiplasmin activity. No spontaneous fibrinolytic activity was observed in any of these persons. A significantly higher antiplasmin level was noted in the patients with myocardial infarction.

Ten subjects with acute myocardial infarction were treated with plasmin infusion. Relief of pain in the chest was noted in eight. Improvement in the T wave and S-T segments observed in five patients immediately following the infusion might be attributed to the infusion. The most common undesirable reaction was pyrexia, which occurred in five patients. Chills, flushes and headache were relatively common. Occasionally, nausea and mild hypotension were also observed. Though the hypotensive and other undesirable side effects deter routine use of this drug in the management of myocardial infarction, the results obtained are encouraging and warrant further observations in a larger series.

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Studies of the Plasmin-Plasminogen System in Thromboembolic Diseases

Its Modifications by Thrombolysin Therapy*

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IN PREVIOUS reports from this laboratory we have described our experiences using plasmin[1,2] in the clinical management of patients with myocardial infarction. Evidence of the existence of increased antifibrinolytic activity or inhibitors of the plasminogen-plasmin system in such patients was also presented. Therefore, we decided to evaluate the efficacy of plasmin as a therapeutic agent in the clinical management of patients with various thromboembolic diseases, to evaluate various parameters of the fibrinolytic system in these disorders and to study the alterations of these factors produced by the infusion of plasmin.

MATERIAL AND METHODS

Studies of fibrinolytic and antifibrinolytic activity were carried out on the following groups: group 1A: eight patients with thromboembolic disease who did not receive plasmin; and group 1B: fourteen patients with thromboembolic disease studied before and after plasmin infusion. These values were compared with those obtained in a control group of twenty-nine normal subjects selected from the resident and laboratory staff, as reported previously.[2]

The following studies were routinely performed upon each of these groups: (1) the lysis time of a standard fibrin clot by undiluted test plasma;[2] (2) the lysis time of a standard fibrin clot by 1:20 dilution of plasmin in imidizole-saline buffer (ISB);[2] and (3) the plasma antiplasmin activity as measured by adding serial concentrations of plasmin‡ to undiluted test plasma and determining the inhibition of lytic activity against a standard clot when compared to similar plasmin concentrations in ISB;[2] and (4) the euglobulin lysis time as determined by precipitation of the euglobulin from the plasma in a manner described by Milstone.[3] The precipitate was redissolved in ISB. This euglobulin solution was tested for lytic activity against a standard fibrin clot.[4] The plasma fibrinogen was determined by the method of Stefanini and Dameshek.[5]

Plasmin was then administered in the following manner: 50,000 or 100,000 Merck units were diluted in 200 ml. of 5 per cent dextrose and water and infused intravenously over a period of thirty minutes to one hour. If the clinical response was inadequate, as manifested by persistence of pain, fever or inflammation, the infusion was repeated every six or eight hours in some instances, or daily for the following three to four days in others. During the course of administration of the drug, the patients were carefully observed and blood pressure, pulse rate and temperature were recorded as often as every fifteen minutes. Serial blood samples were taken and the results of thrombolysin therapy on the fibrinolytic parameters described were studied.

RESULTS

Fibrinolytic Parameters in Patients with Thromboembolic Disease: The results of these studies in group 1A, and in the blood samples from group 1B which were drawn prior to the plasmin therapy, are shown in Table I. It is noted that the plasma fibrinogen is 70 per cent above that of the normal control group. The antiplasmin activity, as determined by clot lysis times of undiluted plasma incubated with 1:10, 1:20 and 1:40 dilutions of plasmin, is approximately

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TABLE I
Fibrinolytic Tests in Untreated Patients with Thromboembolic Disease*

Case No.	Diagnosis	Plasma Fibrinogen (mg./100 ml.)	Antiplasmin Lysis Time (sec.)			Plasma Lysis Time (sec.)		Euglobulin Lysis Time
			Plasmin Diluted 1:10 in ISB	Plasmin Diluted 1:20 in ISB	Plasmin Diluted 1:40 in ISB	Undiluted Plasma	Plasma Diluted 1:20 in ISB	
1	Femoral artery embolism	652	235	937	1,200+	1,200+	347	1,200+
2	Thrombophlebitis + pulmonary infarction	676	331	681	1,200+	...	...	...
3	Thrombophlebitis + pulmonary infarction	786	222	806	1,200+	...	...	...
4	Thrombophlebitis + pulmonary infarction	717	367	908	1,200+	...	...	...
5	Thrombophlebitis + pulmonary infarction	...	...	...	...	1,200+	1,200+	...
6	Thrombophlebitis + pulmonary infarction	...	...	...	...	1,200+	1,200+	...
7	Thrombophlebitis + pulmonary infarction	353	192	471	1,005	...	...	...
8	Thrombophlebitis + pulmonary infarction	342	169	479	1,200+	...	...	...
9	Thrombophlebitis + pulmonary infarction	...	...	...	...	1,200+	1,200+	...
10	Thrombophlebitis + pulmonary infarction	278	376	1,087	1,200+	1,200+	1,200+	...
11	Thrombophlebitis + pulmonary infarction	...	...	...	...	1,200+	1,200+	...
12	Thrombophlebitis + pulmonary infarction	392	251	283	486	1,200+	1,200+	...
13	Thrombophlebitis	465	268	951	1,200+	1,200+	1,064	1,200+
14	Thrombophlebitis	...	372	1,200+	1,200+	1,200+	995	1,200+
15	Thrombophlebitis	621	1,200+	1,200+	1,200+	1,200+	509	1,200+
16	Pulmonary emboli	398	470	1,200+	1,200+	1,200+	1,200+	...
17	Pulmonary emboli	...	...	...	...	1,200+	1,200+	...
18	Pulmonary emboli	547	430	780	1,200+	1,200+	1,200+	...
19	Pulmonary emboli	690	218	1,200+	1,200+	1,200+	1,200+	...
20	Pulmonary emboli	333	QNS	685	1,009	1,200+	1,200+	...
21	Pulmonary emboli	...	398	1,016	1,200+	1,200+	1,200+	...
22	Pulmonary emboli	829	302	612	773	1,200+	1,200+	1,200+
Normal controls†		306 ± 20	211 ± 47	468 ± 146	755 ± 191	1,200+	1,200+	1,200+

NOTE: In this and other tables QNS = quantity not sufficient.
* These case numbers do not refer to the same patients as in Tables II and III.
† A detailed presentation of these data is reported in a previous study.[1]

75 per cent greater than that of the normal control subjects. No spontaneous fibrinolytic activity in this group could be demonstrated in the undiluted plasma. With 1:20 dilutions of plasma in ISB three patients with uncomplicated thrombophlebitis displayed slight spontaneous fibrinolytic activity, evidenced by dissolution of a standard bovine fibrin clot in less than twenty minutes. None of the patients with pulmonary embolism or myocardial infarction displayed such activity.

Effects of Plasmin Therapy: Following administration of plasmin, an increase in fibrinolytic activity was demonstrated by the following tests: The time required for plasma diluted 1:20 in ISB to dissolve a standard fibrin clot was markedly decreased. The antiplasmin lysis times against all three dilutions of plasmin were also noticeably shortened. The clot lysis times of undiluted plasma and the plasma fibrinogen were less affected and frequently remained unchanged. There was considerable

TABLE II

Effects of Plasmin Therapy on Fibrinolytic Tests

Blood Sample	Plasmin Dose (Merck units)*	Time of Sample	Antiplasmin Lysis Time (sec.)			Plasma Lysis Time (sec.)		Euglobulin Lysis Time (sec.)	Fibrinogen (mg. %)
			Plasmin Diluted 1:10 in ISB	Plasmin Diluted 1:20 in ISB	Plasmin Diluted 1:40 in ISB	Undiluted Plasma	Plasma Diluted 1:20 in ISB		
Embolism of the Mid-femoral Artery (Case 6)									
365 (arterial)	None	Before plasmin	235	937	1,200+	1,200+	347	1,200+	656
366 (venous)	100,000 (intra-arterial)	1/2 hr. later	151	434	661	1,200+	430	1,200+	653
367 (arterial)	None	1/2 hr. later	66	135	203	80	287	1,200+	458
386 (venous)	None	24 hr. later	56	154	769	1,200+	1,200+	...	485
406 (venous)	150,000	24 hr. later	62	278	427	1,200+	620	1,200+	452
474 (venous)	None	9 days later	498	1,200+	1,200+	1,200+	641	1,200+	585
Embolism Below Right Popliteal Artery (Case 4)									
254	200,000	1/2 hr. later	153	325	621	1,200+	1,200+	924	439
255	200,000	1 hr. later	124	290	480	1,200+	1,109	1,031	438
256	None	2 hr. later	96	275	459	1,200+	1,200+	916	...
280	None	48 hr. later	148	633	912	1,200+	1,010	1,200+	556
281	200,000	2 hr. later	No clot	No clot	No clot	1,200+	333	1,243	524
282	None	24 hr. later	93	373	701	1,200+	1,200+	1,200+	684
283	200,000	2 hr. later	No clot	No clot	No clot	343	216	1,200+	444
371	None	24 hr. later	122	321	744	1,200+	183	1,200+	599
372	200,000	2 hr. later	No clot	No clot	No clot	No clot	220	671	533
373	None	24 hr. later	104	295	621	1,200+	1,200+	1,200+	584
Thrombophlebitis, Right Leg and Pulmonary Embolism (Case 8)									
491	None	Before plasmin	94	293	524	700	451	...	283
492	150,000	10 min. later	No clot	90	395	82	256	405	235
497	None	1 hr. later	No clot	184	235	103	270	418	281
510	None	3 hr. later	No clot	174	403	120	288	820	203
Pulmonary Embolism (Case 5)									
251	None	Before plasmin	QNS	685	1,009	1,200+	1,200+	1,200+	333
252	50,000	1 hr. later	122	331	596	1,200+	1,200+	1,200+	572
253	100,000	5 hr. later	71	387	574	1,200+	1,200+	1,200+	390
260	None	24 hr. later	225	795	1,200+	1,200+	769	1,200+	717
261	100,000	5 min. later	83	465	582	1,200+	1,233	1,076	527
Thrombophlebitis, Right Leg (Case 2)									
744	None	Before plasmin	372	1,200+	1,200+	1,200+	995	1,200+	...
745	150,000	1/2 hr. later	267	1,200+	1,200+	...	323	1,088	412
746	None	24 hr. later	279	1,200	1,200	1,200+	830	1,200+	556
747	125,000	1/2 hr. later	242	1,057	1,200+	1,200+	403	1,200+	551
770	None	5 hr. later	235	1,022	1,200+	1,200+	934	1,200+	562
771	125,000	1/2 hr. later	122	463	1,043	50	384	1,200+	412
785	None	24 hr. later	49	111	596	1,200+	676	1,200+	520
786	150,000	1/2 hr. later	No clot	No clot	No clot	93	231	1,005	478
828	None	4 days later	48	194	374	1,200+	288	1,200+	478
829	100,000	1/2 hr. later	No clot	No clot	No clot	95	250	717	433
Thrombophlebitis, Left Leg (Case 3)									
560	None	Before plasmin	1,200+	1,200+	1,200+	1,200+	509	1,200+	621
561	100,000	5 min. later	1,200+	1,200+	1,200+	311	181	908	600
562	None	1 hr. later	1,200+	1,200+	1,200+	711	279	958	621
563	None	3 hr. later	1,200+	1,200+	1,200+	753	272	1,081	623
564	None	21 hr. later	1,200+	1,200+	1,200+	824	330	1,153	733
576	100,000	5 min. later	499	1,200+	QNS	166	127	1,118	621
578	None	3 hr. later	515	1,200+	QNS	870	361	1,200+	621
579	None	24 hr. later	708	1,200+	1,200+	870	415	1,200+	690

TABLE II—*Continued*

Blood Sample	Plasmin Dose (Merck units)*	Time of Sample	Antiplasmin Lysis Time (sec.)			Plasma Lysis Time (sec.)		Euglobulin Lysis Time (sec.)	Fibrinogen (mg. %)
			Plasmin Diluted 1:10 in ISB	Plasmin Diluted 1:20 in ISB	Plasmin Diluted 1:40 in ISB	Undiluted Plasma	Plasma Diluted 1:20 in ISB		
Myocardial Infarction†									
PAS 1	None	Before plasmin	No clot	No clot	No clot	No clot	398	997	...
PAS 2	200,000	½ hr. later	No clot	No clot	No clot	No clot	98	801	235
PAS 3	None	12 hr. later	No clot	No clot	No clot	No clot	330	QNS	...
PAS 4	200,000	½ hr. later	No clot	No clot	No clot	No clot	206	805	...
R.B. 8	None	Before plasmin	110	255	427	1,200+	1,033	1,182	456
R.B. 9	200,000	1 hr. later	103	275	445	1,190	1,033	272	433
R.B. 10	None	24 hr. later	80	364	485	1,200+	906	715	653
R.B. 11	200,000	½ hr. later	78	304	509	1,200+	1,200+	214	621
R.B. 12	None	12 hr. later	96	310	396	...	...	344	561
R.B. 13	200,000	½ hr. later	173	636	871	...	...	297	498
M. 1	None	Before plasmin	No clot	No clot	No clot	1,200+	660	1,200+	...
M. 2	200,000	½ hr. later	No clot	No clot	No clot	88	298	422	...
M. 3	None	½ hr. later	No clot	No clot	No clot	85	368	1,200+	...
M. 4	200,000	½ hr. later	No clot	No clot	No clot	84	331	418	...
M. 5	None	½ hr. later	No clot	No clot	No clot	74	436	1,200+	...
M. 6	200,000	½ hr. later	No clot	No clot	No clot	No clot	292	1,200+	...
M. 7	None	12 hr. later	No clot	No clot	No clot	59	121	1,200+	...
M. 8	200,000	½ hr. later	No clot	No clot	No clot	51	191	742	...
M. 9	None	12 hr. later	No clot	No clot	No clot	53	176	1,200+	...
M. 10	200,000	½ hr. later	No clot	No clot	No clot	No clot	269	1,200+	...
Pulmonary Embolism†									
145	None	Before plasmin	302	612	773	1,200+	1,200+	1,200+	868
147	200,000	Immediately after	No clot	No clot	140	184	608	620	850
149	None	1½ hr. later	No clot	No clot	170	186	712	630	860
151	None	12 hr. later	64	113	466	209	934	643	854
153	200,000	Immediately after	No clot	60	94	No clot	508	470	835
160	None	3 hr. later	78	110	309	No clot	539	836	850
167	100,000	12 hr. later	62	128	364	No clot	764	1,200+	QNS

* Administered intravenously unless otherwise indicated.
† These samples were taken from patients whose clinical course is not recorded in Table II.

variation in the response of patients with the same disease to the administration of equal concentrations of plasmin (Table II).

Clinical Results of Plasmin Therapy: Table III illustrates the clinical course of patients with thromboembolic phenomena who were treated with plasmin. Dramatic relief of pain was observed in four of five patients with acute thrombophlebitis within a few hours after administration of the drug. In the fifth patient in whom treatment was instituted fourteen days after onset of the disease, the drug was ineffectual.

This therapy appeared to be effectual in three of four instances of pulmonary embolism. Significant relief of pain in the chest was noted in one patient one hour after the infusion of plasmin. Pain disappeared completely in twenty-four hours. All traces of hemoptysis were gone within thirty-six hours. Fever dropped rapidly and rales diminished in another patient. Similar improvement and relief of pain for a period of ten days following the administration of plasmin was observed in a third patient. In a fourth, critically ill patient, however, this treatment proved ineffectual. He died twenty-four hours after administration of plasmin and at autopsy multiple emboli were found. In the remaining cases of thromboembolic disease the number of patients was too small to differentiate the natural history and variability of the disease process from symptomatic changes due directly to the administration of plasmin.

Side Effects: Elevation of temperature from 1° to 5°F. and hot flushes were the most frequently observed adverse effects definitely due to the administration of plasmin. These occurred in approximately 33 per cent of the patients. In only two instances did the temperature reach 100.5°F. or above. Blood

TABLE III
Clinical Course of Patients Treated with Plasmin

Case No.	Age and Sex	Date of Onset (1959)	Diagnosis and Clinical Status	Date of Administration (1959)	Dose (Merck units)	Reactions			Results
						Temperature (°F.)	Blood Pressure (mm. Hg)	Pulse (beats per min.)	
1	48, F	2/15	Thrombophlebitis, right leg; still inflammatory	2/24	100,000	98 103 in 3 hr.; chills lasted 12 hr.	130/86 130/86	65 90	Within a few hours significant relief of pain and local tenderness; because of fever, therapy stopped
2	50, F	3/17	Thrombophlebitis, right leg; still inflammatory	3/24 3/25 3/26 3/30	150,000 125,000 150,000 150,000	99 101; Flushes Flushes Flushes	130/80 118/76	70 70	Within a few hours relief of pain; inflammation subsided; color normal
3	60, M	5/14	Thrombophlebitis, left leg; acute phase	5/15 5/16	100,000 200,000	98 100.2	110/70 110/60	78 72	Relief of pain within a few hours; inflammation subsequently subsided; leg almost normal
4	87, M	2/15	Arterial occlusion below right popliteal artery; acute phase	2/16 2/17 2/18 2/19 2/20	200,000 200,000 200,000 200,000 200,000	Unchanged Unchanged Unchanged Unchanged Unchanged			One or 2 hr. after plasmin administration pedal pulses became palpable and feet warmer; within the next few days leg became gangrenous and was amputated
5	62, M	2/15	Pulmonary embolism	2/16 2/17	150,000 100,000	Unchanged Unchanged			Impressive improvement; fever decreased; auscultatory findings diminished
6	58, M	2/21	Arterial occlusion; middle right femoral artery	2/25 2/26 2/26	100,000 into artery 100,000 IV 50,000	Unchanged			Immediate feeling of relief from pain; foot warmer; leg amputated after 8 days
7	35, M	4/11	Pulmonary embolus; thrombophlebitis; critical state	4/12	150,000	Unchanged			Patient died 24 hr. later; autopsy revealed multiple emboli
8	66, M	4/24	Thrombophlebitis; still inflammatory	5/8	150,000	Unchanged			No noticeable change
9	55, M	11/15	Status anginosis; impending infarction	11/16 11/16	Poor fibrinolytic activity Plasmin from another source	Unchanged Dropped during 2nd infusion			Died during second infusion of plasmin, within 24 hr. of admission
10	78, F	4/22	Hemiplegia	4/23 4/24	200,000 200,000 200,000 200,000	99.4 101 102	180/120 170/110 150/100		No demonstrable change; died three days later
11	87, F	3/24	Hemiplegia	3/25 3/26	200,000 300,000				Thirty minutes after plasmin therapy moved right arm for first time; died three days later
12	53, M	1/9	Thrombosis, subclavian veins; pulmonary embolism	1/6 1/7 1/9 1/10 1/11	40,000 40,000 40,000 40,000 40,000		140/90 130/90		Relieved of pain for 10 days following therapy
13	60, M	4/20	Myocardial infarction; in shock	4/20	100,000				Pulse faster, blood pressure dropped; died within 10 min. of receiving slow infusion of plasmin
14	70, M	11/11	Myocardial infarction	11/11	100,000				Patient died 24 hr. later
15	34, M	11/9	Pulmonary embolus	11/10 11/11 11/11 11/12	200,000 200,000 100,000 200,000	Unchanged			Within 1 hr. significant relief of pain in the chest; pain disappeared in 24 hr.; hemoptysis disappeared in 36 hr.

pressure and pulse rate were not usually affected. Hemorrhagic diatheses or recurrence of thrombophlebitic episodes were not noted during the course of the therapy.

Comments

Abnormalities of the Fibrinolytic System in Thromboembolic States: The decrease in fibrinolytic activity noted in the acute phases of various thromboembolic disorders is of considerable theoretical and practical significance, since it tends to amplify our knowledge of the intravascular coagulation mechanisms and aids in obtaining a rational approach to the treatment of these diseases. The coexistence of increased fibrinogen levels and antifibrinolytic activity noted in this study has also been observed by Guest and co-workers[6] in patients with acute streptococcal infections, acute bacterial endocarditis, cirrhosis of the liver and coronary thrombosis. Shulman[4] described a parallel elevation of plasma fibrinogen and trypsin inhibitor in patients with tissue necrosis but found little evidence of antiplasmin activity. This paradox can be partially reconciled by the now established existence of more than one inhibitor of the plasmin-plasminogen system in the blood.[7–9]

Changes in Fibrinolytic Parameters Following Plasmin Administration: After the administration of plasmin there was increased fibrinolytic activity in most of the patients, demonstrated by a shortening of clot lysis time of plasma diluted to 1:20 with ISB.

The decrease in inhibitor activity observed in the blood of most patients following administration of plasmin, the variability in response of patients with the same disorder to the administration of fixed dosages of plasmin and the enhanced ability of the blood of patients receiving frequent large doses of plasmin to dissolve fibrin clots *in vitro*, testify not only to the rationale of plasmin therapy in these disorders but also to the difficulty of arriving at a fixed dosage schedule. With the advent of more purified preparations of plasmin we have been able to administer the drug in progressively larger doses and at more frequent intervals, but the optimum dosage schedule has not yet been obtained. Plasma fibrinogen concentrations did not change rapidly enough to reflect the sudden increases in fibrinolytic activity found in the blood of our patients subsequent to the administration of plasmin. Similar observations were noted by Sherry and his co-workers.[10] When they administered electroshock therapy to several patients, they found increased fibrinolytic activity as measured by euglobulin lysis time and whole blood lysis time, although the plasma fibrinogen remained unchanged.

Significance of Therapeutic Effects of Plasmin in Thromboembolic States: In this limited series caution in evaluating the effectiveness of plasmin is necessary because of the protean manifestations of the natural history of these disorders. Nevertheless, in a number of patients, clinical improvement following plasmin therapy was sufficiently striking to suggest a cause and effect relationship. The patients in our series fall into three groups: (1) eight patients in whom the coincidence of clinical improvement and enhanced fibrinolytic activity is clear cut; (2) three patients in whom the alterations in the clinical course of the disease were not sufficiently distinctive to indicate plasmin as the etiologic agent, despite enhancement of fibrinolysis *in vitro;* and (3) six critically ill patients whose clinical state deteriorated so soon after the administration of plasmin that it was difficult to differentiate the natural course of the disease from complications produced by infusion of the drug.

Our results in the management of patients with acute thrombophlebitis confirm those of Cliffton,[11] Moser[12] and Ambrus.[13] When plasmin was administered within the first forty-eight hours after the onset of symptoms, there was marked clinical improvement, demonstrated by relief of pain and disappearance of local heat and tenderness. The effectiveness of plasmin therapy diminished greatly if there was a delay of several days between onset of symptoms and the administration of the drug. In the remaining thromboembolic states, the series was too limited to draw definite conclusions.

Present Role of Proteolytic Enzymes in the Treatment of Thromboembolic Disease: In recent years proteolytic enzymes have been under intense investigation in attempts to produce lysis of thrombi.[11,12,14,15] The most promising therapeutic approaches utilize either potent activators of human plasminogen such as streptokinase, or the active enzyme itself, plasmin. Early studies with Varidase,® which contained a partially purified streptokinase, revealed that this drug was capable of liquefying thrombi. Unfortunately, this preparation was highly antigenic and was accompanied by pyrogenic and hypotensive reactions.[16] Fletcher and co-workers[14,15] recently investigated a highly puri-

fied streptokinase and reported a marked decrease in such reactions. By rapidly activating the body plasminogen to plasmin, a potent fibrinolytic state was produced which readily dissolved thrombi. The increased antithrombin activity and decreased Ac globulin caused by this infusion resulted in a prolongation of the prothrombin time and a state of hypocoagulability in some patients in whom blood tended to ooze from puncture sites and in whom ecchymoses developed at other injection sites.

The use of plasmin, the activated enzyme, was the mode of therapy employed in our study. With this drug, also, earlier preparations were found to be effective in lysing thrombi but highly pyrogenic.[11] In the present group of patients, as compared with the first six patients with myocardial infarction treated with an earlier preparation of plasmin,[2] it may be noted that there was a considerable decrease in severe pyrogenic reactions. It is difficult to predict whether the activators of plasminogen or plasmin itself will prove to be the treatment of choice in the management of thromboembolic diseases.

Evidence supports the view that fibrinolysis is a basic physiologic process controlled by activators stimulating increased lytic activity and inhibitors preventing excessive fibrinolysis in the organism. Kwaan, Lo and McFadzean,[17] as well as Sherry,[10] have presented evidence that a neurogenic mechanism might mediate the production of fibrinolytic activity. Although Astrup[18] and Duguid[19] have recently speculated on the possible relationship of fibrinolysis to the development of atherosclerosis, more experimental work is needed for these hypotheses to gain wide acceptance.

Summary

Blood samples from twenty-two patients with thromboembolic disease were studied using the following tests: plasma fibrinogen, clot lysis by undiluted and diluted plasma, euglobulin lysis time and antiplasmin activity. Plasmin was administered later to fourteen of these patients. The plasma fibrinogen and antiplasmin activity were approximately 70 per cent higher in patients with thromboembolic disease than the levels of activity in normal control subjects. Following the administration of plasmin, antiplasmin activity and clot lysis time in diluted plasma declined sharply, but the plasma fibrinogen was only slightly diminished. Plasmin therapy was most effective in acute thrombophlebitic states of recent origin. Elevation of temperature and hot flushes were the most frequently encountered adverse reactions.

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Experimental Study

Peripheral Distribution of the Canine A-V Conduction System

Observations on Gross Morphology*

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MANY OF THE basic concepts of electrocardiography are based on the existence of an anatomically and physiologically distinct A-V conduction system. Although the presence of a distinct system has been challenged in recent years,[1–3] its existence with certain variations in man and other species is generally accepted.[4–7]

The dog has been frequently used for electrocardiographic study, and consequently basic knowledge of its A-V conduction system is of importance. Studies of the canine conduction system have been made involving gross dissection, microscopic study with special stains and wax reconstruction.[8] However, the peripheral distribution of the conduction system remained somewhat less accessible to study by the usual technics. On the other hand, the presence of increased concentration of glycogen in the conduction system[9] affords a means by which Purkinje tissue may be distinguished from ordinary myocardial fibers. By means of glycogen staining it was possible to study the details of the major portion of the A-V conduction system of the dog. This paper reports these observations.

METHODS

The use of iodine staining for glycogen is an established histologic technic,[10] and the application of iodine as a gross indicator of the conduction system of the dog[11,12] and man[13] has been described.

In this study, hearts were removed from thirty dogs, opened to expose the left and right ventricular septum and washed with water. Lugol's solution applied to the endocardial surfaces with a cotton swab or an eye dropper brought out a vast bluish-brown network. X-ray studies of hearts in which a radio-opaque medium was injected into the arterial system (Schlesinger's technic[14]) demonstrated that the stained network was not part of the vascular tree. Histologic study with Best's carmine confirmed that the stained structures were rich in glycogen. The specimens were photographed and studied.

RESULTS

The Left Bundle of the A-V Conduction System: The left bundle of the dog's conduction system appears as a broad band on the left surface of the septum in the area inferior to the membranous septum beneath the commissure between the posterior and right cusps of the aortic valve (Fig. 1). The bundle immediately divides into two primary branches going toward the anterior and posterior papillary muscles. The anterior primary branch generally follows a more horizontal course and emerges from the septal wall about two-thirds of the way to the anterior papillary muscle. The posterior primary branch courses more inferiorly and emerges from the septal wall mid-way to the posterior papillary muscle. Both of these primary branches divide into smaller branches near the papillary muscles, and several of these

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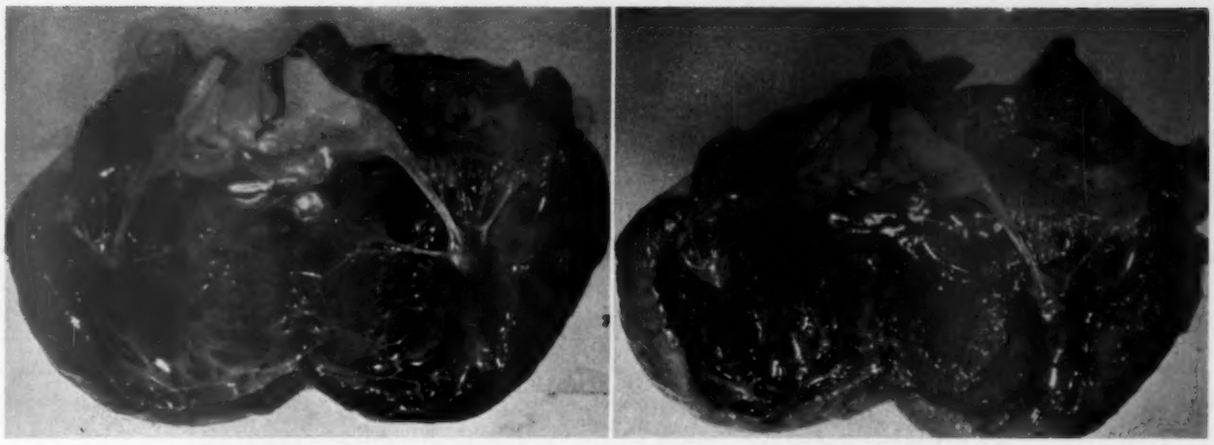


A B

FIG. 1. A, heart of a dog opened to expose the left ventricular septum. B, same heart as in Figure 1A, stained with Lugol's solution to bring out the conduction system.

smaller branches sweep around the papillary muscles to the lateral wall of the left ventricle. In addition to these branches, there is a vast network of fibers extending between the aforementioned anterior and posterior primary branches blanketing the subendocardium of the septum (Fig. 2).

In comparing the photographs of the stained and unstained hearts (Fig. 1), it is apparent that many of the strands seen on the unstained heart are, in effect, portions of the peripheral and terminal branches of the conduction system (Purkinje fibers).

The Right Bundle of the A-V Conduction System: On the right side of the heart the right bundle of His appears beneath the medial leaflet of the tricuspid valve, inferior to the membranous septum. The fibers continue anteriorly and

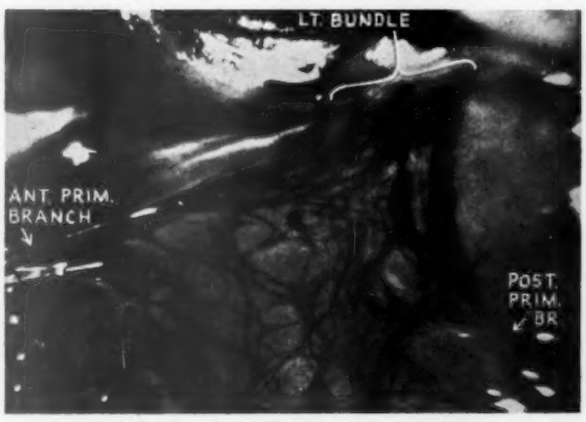


FIG. 2. Close-up photograph of the stained left branch of the bundle of His as it emerges on the left side of the interventricular septum (*arrow*), showing its separation into anterior and posterior primary branches and numerous ramifications.

inferiorly without branching until half-way down the septum at which point the bundle deviates inferiorly (Fig. 3). A second bend then directs the bundle posteriorly, placing it just anterior to the anterior papillary muscle. In this region, the bundle divides into primary groups of branches.

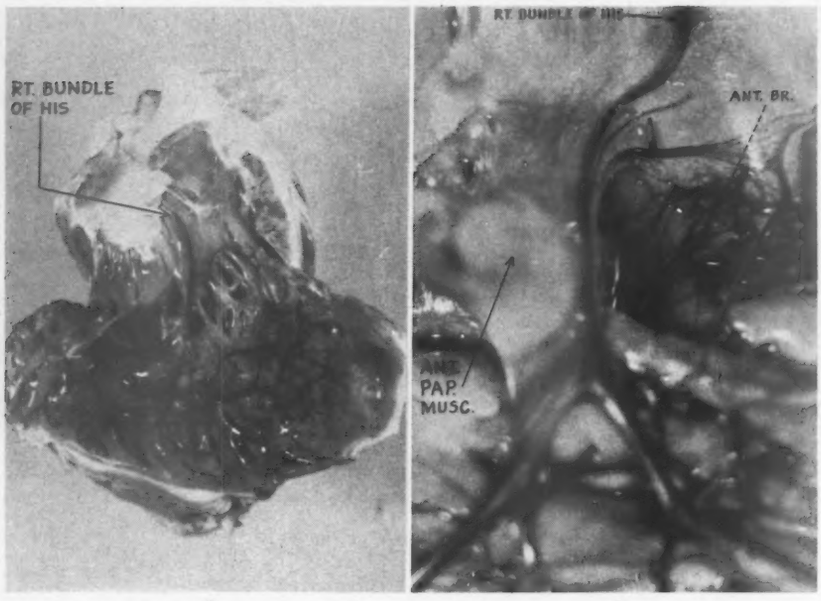
The anterior primary branches are small and proceed anteriorly on the inferior septal wall ramifying along the trabeculae carneae of the anterior right ventricular wall. They also supply the lower one-third of the anterior part of the septum (Fig. 4).

The lateral primary branches are the largest peripheral branches of the right bundle and appear as two or more main trunks radiating from the anterior surface of the base of the anterior papillary muscle to the right ventricular wall. The trunks extend superiorly to supply a rich network of Purkinje fibers for most of the right ventricular wall (Fig. 5).

The smaller posterior primary branches proceed posteriorly along the septum from the base of the anterior papillary muscle to the posterior papillary muscle, from which point small branches are supplied to the posterior right ventricular wall. Branches may pass on both mural and septal sides of the anterior papillary muscle. As with the anterior primary branches, the posterior primary branches have a comparatively minor distribution on the ventricular septum in contrast to their distribution on the right ventricular wall.

COMMENTS

Examination of the stained left ventricular septal surface (Fig. 2) discloses an extensive



3 4

FIG. 3. Right ventricle exposed to show the stained right bundle of His (*arrow*) and its branches.

FIG. 4. Close-up of the region around the anterior papillary muscle of the right ventricle showing the stained right bundle of His separating into branches. Note the confinement of the anterior primary branches of the right bundle to the lower portion of the septal wall.

network of conduction tissue over the septal myocardium. Examination of the corresponding right ventricular septum reveals that while a dense concentration of glycogen-rich fibers is present on the inferior portion, there is a lack of fibers in the mid- and upper endocardial surfaces. In studies of the activation of the dog's septum,[15–17] it has been found that the earliest signs of activity are on the left side of the septum, which is the area in which the density of glycogen-rich fibers is greatest. The earliest activity on the right side of the heart is at the junction of the mural and septal walls. Anatomically this is the same area in which the first branches of the main right bundle

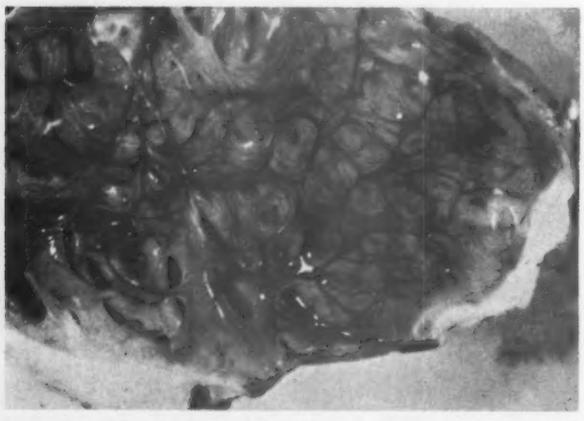


FIG. 5. Close-up of the stained endocardial surface of the right ventricular wall showing the extensive network of conduction fibers radiating from the lateral primary branches of the right bundle (upper left portion of photo).

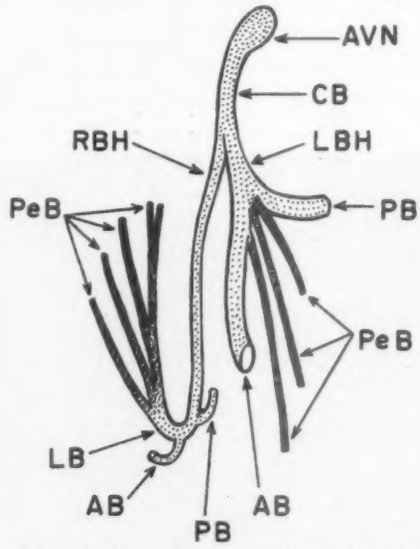


FIG. 6. Suggested representation of the A-V conduction system of the dog. AVN is the A-V node; CB is the common bundle; RBH and LBH are the right and left bundles of His; AB, LB and PB are the anterior, lateral and posterior primary branches; PeB are peripheral branches.

are seen. Thus there seems to be a correlation between the concentration of conduction tissue on the septum and the earliest sites of electrical activity. The mid- and upper right septum and the extreme superior portions of the left septum are devoid of stained fibers and are also late sites of electrical activity.

On the basis of these studies it would appear that the A-V conduction system might best be pictorially represented by the drawing in Figure 6 instead of the conventional representation of a common bundle simply separating into a left branch and a right branch.

It would seem that a small lesion of the mid- or lower septal surface would be more likely to cause a right-sided defect if it were in the path of the right bundle than a corresponding defect in the path of the left bundle, because of the multiple opportunities for bypassing the lesion afforded by the extensive network of the left bundle. Perhaps this anatomic distribution bears some relationship to the relative frequency of right bundle branch block seen clinically,[18] assuming there is a basic similarity in the canine and human conduction systems.

Summary

The conduction system of dog hearts was visualized by Lugol's staining of the endocardial surface.

The left bundle of His appears as a broad band on the left ventricular septum which separates into anterior and posterior primary branches to the respective papillary muscles and a rich network supplying the remaining septal and free wall musculature.

The right bundle appears on the right septum as a long narrow band extending to the anterior papillary muscle where it forms anterior primary branches, several large lateral primary branches and posterior primary branches. These branches ramify extensively over the free right ventricular wall.

The areas of the ventricular septum which are activated early have a rich concentration of glycogen-staining fibers, and the areas which are activated late (mid- and upper right septal surface and the extreme superior portions of the left septal surface) are relatively free of glycogen-staining tissue.

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Review

Diagnostic and Pathogenic Borderlines Between Hypertensive Disease and Atherosclerosis*

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THE FREQUENT coexistence of hypertensive disease and atherosclerosis is generally known. The following account will show that this common coexistence is not an accidental one. According to the records of the Institute of Therapy of the Academy of the Medical Sciences of the U.S.S.R., the incidence of hypertension in the population averages 5 per cent; in the older age groups the percentage is higher: between forty and forty-nine years of age it amounts to 9 per cent, between fifty and seventy years of age to 26 per cent. On the other hand, arterial hypertension exists in cases of atherosclerosis (especially of the coronary arteries) in 30 per cent of the group of patients forty to forty-nine years old, and in 50 per cent of those fifty to seventy years of age. Thus, on an average, hypertension occurs among atherosclerotic patients three times as frequently as in the same total age groups.

Naturally, the diagnosis of atherosclerosis from the presence of coronary sclerosis can be made only as an approximation. The question arises as to the nature of the interrelations between hypertension and atherosclerosis which are responsible for their frequent coincidence.

DIFFICULTIES IN DIFFERENTIATION OF HYPERTENSIVE DISEASE AND ATHEROSCLEROSIS

Before approaching this question, however, we shall direct our attention to another aspect of the problem, namely, the difficulties in differentiating between hypertensive disease and atherosclerosis. We do not mean by this the recognition of the presence of an elevated blood pressure *per se*. The difficulty of separating hypertensive disease from atherosclerosis can be illustrated by many examples.

HEREDITARY-FAMILIAL FACTORS

We shall first discuss data concerning hereditary-familial factors. In the Institute of Therapy, a study has been conducted for several years dealing with the occurrence of hypertensive disease and of atherosclerosis in the families of patients. The staff members of the Institute, S. J. Bitkova, N. K. Belyaeva, E. V. Soolye, and others have found that in the families of hypertensive patients hypertension was encountered two and a half times more frequently than in the families which were used as controls (Table 1). This study also revealed that, in addition to hypertension, signs of coronary sclerosis (myocardial infarction) were likewise more common in the aforementioned families than in the control families.

By selecting the families of atherosclerotic patients, our co-workers have ascertained that among the members of these families atherosclerosis was present twice as frequently as in the control families; the number of persons with hypertension in these families was even higher. Thus, it can be stated that in the families of patients with vascular disease—whether they had hypertension or atherosclerosis—both conditions were encountered with a sig-

* This paper was translated from the Russian original by W. Raab, M.D., F.A.C.C., Burlington, Vermont.
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TABLE:

Incidence of Hypertension and of Hypertension with Atherosclerosis in Families of Hypertensive Patients and Control Group

Group	No. of Families	No. of Family Members over 30 Years of Age	Hypertensive Patients			
			Total		Hypertension Alone (No.)	Hypertension and Atherosclerosis (No.)
			No.	%		
Families of hypertensive patients	184	463	261	56.4	194	67
Families of control group	80	230	50	21.7	30	20

nificantly greater frequency than in the non-selected control group. Furthermore, it was concluded that both types of vascular disease have the same familial-hereditary background (Table 1).

Figures 1 and 2 illustrate, by different examples, the remarkable analogies between hypertension and atherosclerosis with respect to familial-hereditary interrelations. Our conclusions are in agreement with general medical experience, according to which the family history of hypertensive patients often reveals the presence of both hypertension and atherosclerosis, and that of atherosclerotic patients reveals the presence not only of atherosclerosis but also of hypertension.

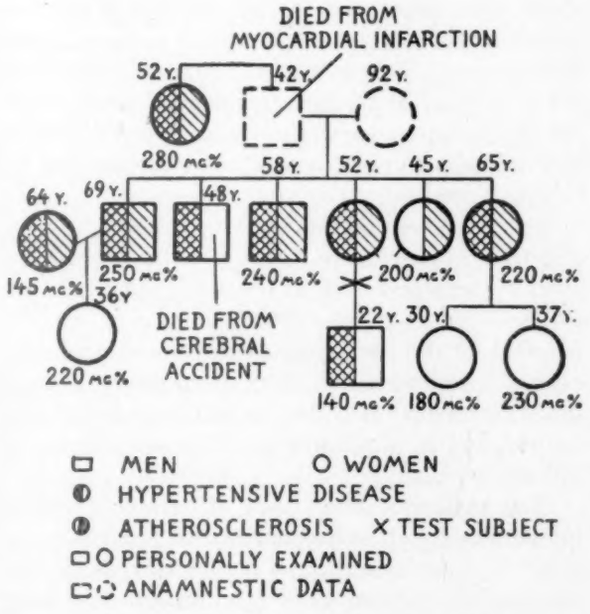

FIG. 1. Diagram of the results of examination and history-taking of family members of a fifty-two year old patient who had hypertensive disease in the second stage.

DEVELOPMENTAL DYNAMICS

A comparison of the developmental dynamics of the two morbid entities may serve as the second example to illustrate the difficulty of differentiating between them. All of us have been taught the old concept of Yooshar which interpreted hypertension as a presclerotic condition. The neurogenic theory of hypertension, however, suggests that this disease displays at the begin-

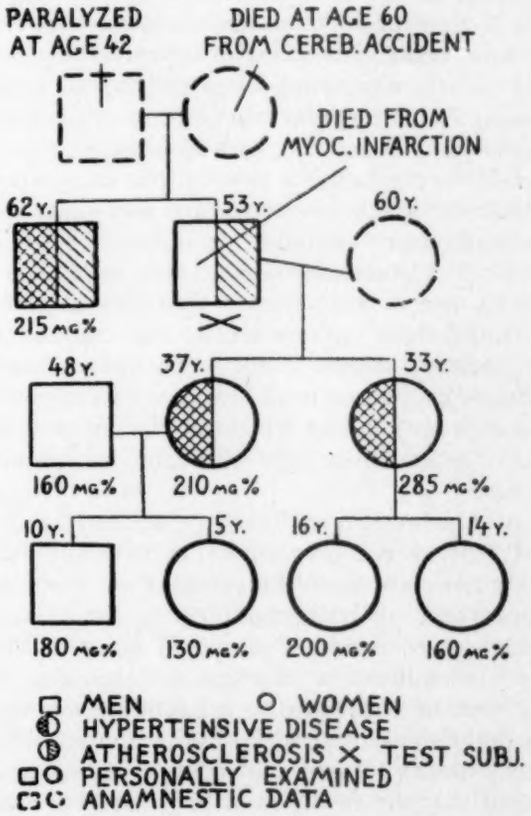

FIG. 2. Diagram of the results of examination and history-taking of family members of a fifty-three year old patient who had coronary atherosclerosis and angina pectoris.

ning a reversible, purely functional, character and that signs of atherosclerosis develop only at a later stage. It is also generally known that atherosclerosis is often encountered without hypertension, even together with a low blood pressure, and that atherosclerosis may be observed before hypertension makes its appearance. It must be admitted that the question of the real relation between the initial stage of both hypertension and atherosclerosis is particularly difficult to answer due to the fact that, as a rule, the early manifestations of both diseases are not sufficiently distinct. Hypertensive disease may exist for many years without producing any unpleasant subjective sensations, and the diagnosis is often made only when blood pressure is measured. As far as atherosclerosis is concerned, a myocardial infarction serves not infrequently as its "first" symptom. Unfortunately, it is often also the last one.

Data concerning the gradual development of both conditions can be obtained only by means of entirely heterogeneous and poorly comparable methods. Thus, clinical observation may reveal early hypertensive reactions (vascular hyperreactivity which is often noticed at a young age, without being identical with hypertension *per se*, but rather constituting its prelude). In recent times, an earlier development of the disease has become noticeable, with its beginning at the age of twenty to thirty years. The early manifestations of atherosclerosis are accessible only to pathologic anatomic examination (which shows that lipoidosis exists as early as the age of twenty-five to thirty years—not to be regarded as full-fledged atherosclerosis but only as its preliminary stage). Thus, the roots of both diseases may reach back into the years of youth, but it is not clear at which point their premorbid stages assume the character of genuine disease.

At the Institute of Therapy, patients admitted with a combination of hypertension and atherosclerosis gave histories of a successive appearance of both conditions. *The following features were interpreted as criteria of atherosclerosis:* intensification of anginal symptoms, occurrence of a myocardial infarction, and myocardial damage with atrial fibrillation and other arrhythmias. Forty per cent of all patients stated that the elevation of their blood pressure had preceded the appearance of atherosclerotic manifestations; 25 per cent affirmed that they had noted signs of atherosclerosis earlier, while hypertension was discovered subsequently; 35 per cent were unable to answer the respective questions or claimed that both diseases had been diagnosed at the same time. Not infrequently, patients with a myocardial infarction reported that for several months or days before the development of coronary symptoms, they had suffered from hypertension which then subsided. It thus follows that it is difficult to draw a line between the two conditions as regards the time of their onset.

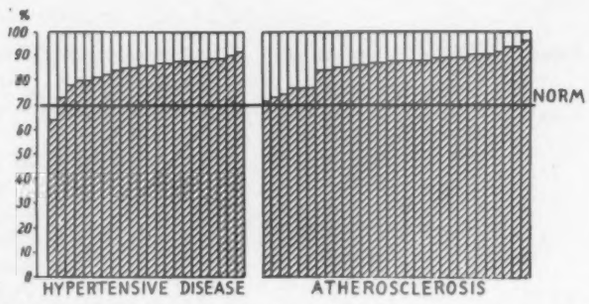

FIG. 3. Percentile distribution of serum beta- and alpha-lipoproteins of patients with hypertensive disease and atherosclerosis. Each bar represents one patient. Only men fifty to fifty-five years of age are included. *Shaded columns:* beta-lipoproteins. *White columns:* alpha-lipoproteins.

BIOCHEMICAL DIFFERENTIATION

A third example is the *biochemical differentiation of the two diseases.* At present it is generally accepted that atherosclerosis is characterized by a tendency toward hypercholesterolemia as well as toward a lowering of the phospholipid: cholesterol ratio, and by an increase of the so-called beta-lipoproteins in the plasma. However, among hypertensive patients, there are many with hypercholesterolemia and, surprisingly, the occurrence of hypercholesterolemia is nearly identical in hypertensive disease and in atherosclerosis.

Several investigators have pointed out a frequent augmentation of the beta-lipoprotein level in the blood. If, as is usually assumed, the presence of hypercholesterolemia and an alteration of the lipoproteins suggests the coexistence of atherosclerosis in hypertensive disease, it would seem that it should be encountered less frequently in hypertensive disease than in atherosclerosis.

Our material shows that (1) the numerical incidence of hypercholesterolemia is almost the same in both diseases; (2) the degree of increase of the cholesterol level is undoubtedly more significant in atherosclerosis; and (3) beta-lipoproteins are augmented in the blood in both atherosclerosis and hypertension (Fig. 3). Ob-

TABLE II

Blood Cholesterol in Normotensive Members (Older Than Thirty Years of Age) of Families of Hypertensive Patients and Control Group

Group	No. of Persons Examined	Blood Cholesterol Levels		Incidence of Elevated Cholesterol (%)
		Normal No.	Elevated No.	
Family members of hypertensive patients	168	117	51	30.3
Family members of control group	211	174	37	17.5

servations of our co-workers (particularly of E. P. Fedorova) concerning the blood cholesterol levels of members of families of hypertensive and atherosclerotic patients are of interest. An increase of the blood cholesterol was frequently discovered in persons in whom, until the time of the blood testing, neither an elevation of the blood pressure nor any signs of atherosclerosis had been noticed (Table II).

It is surprising how tightly interwoven these features appear on examination of the families of patients suffering from vascular disease, namely, hypertension, hypercholesterolemia and signs of atherosclerosis. In these families, hypercholesterolemia is found more commonly than in those of the control families, frequently even at a young age. Our data permit the conclusion that the metabolic disturbances to which we attribute such a great importance in the origin of atherosclerosis constitute a significant link between atherosclerosis and hypertension.

CARDIAC COMPLICATIONS OF HYPERTENSION AND ATHEROSCLEROSIS

A fourth example of the difficulty in establishing diagnostic borderlines between hypertensive disease and atherosclerosis is to be found in the number of *cardiac disorders that occur in these diseases.*

Cardiac Hypertrophy: Hypertrophy of the left ventricle, an early and typical sign of hypertension, occurs in its earlier forms also with atherosclerosis. It is known that there are at least two causes for hypertrophy of the left ventricle in connection with atherosclerosis: (1) sclerotic alterations of the aorta and other large vessels which reduce their elasticity, thus adding to the burden of the heart; and (2) the ischemia-producing influence of coronary sclerosis upon the myocardium which, as is now well established, elicits a reactive hypertrophy of the myocardial fibers. It is no wonder that both diseases have the phenomenon of cardiac hypertrophy in common, if one takes into consideration that both of the two aforementioned factors are also present in hypertension, namely, an increased strain on the heart due to augmented arterial pressure, and myocardial ischemia due to hypertensive narrowing of the coronary vessels.

Electrocardiogram: It is not easy to differentiate the hypertensive from the atherosclerotic heart by means of electrocardiography (speaking of the earlier stage). We know that a downward displacement of the S-T segment, suggesting a major or minor degree of coronary insufficiency, is a common characteristic of both diseases. The prerequisites for myocardial ischemia, either relative (due to cardiac hypertrophy), or absolute (due to atherosclerotic or hypertensive narrowing of the coronary arteries), exist in both atherosclerosis and hypertension. Of course, focal phenomena are more characteristic for atherosclerotic and less characteristic for hypertensive disease, but the formation of ischemic foci as a result of hypertensive spasms of the coronary vessels cannot be ruled out. Although it is almost certain that myocardial infarction develops on the basis of coronary atherosclerosis, it does not take place without the contribution of functional vasomotor disturbances and, thus, it may be said that its occurrence is due to the interaction of two factors: atherosclerotic vascular narrowing and vasomotor reaction.

Ballistocardiogram: Ballistocardiographic observations in both types of vascular disease are instructive. In the Institute of Therapy, Aspirant Lin Chen has stated that alterations of the ballistocardiogram, indicative of derangements of the contractile function of the heart, are encountered with increasing frequency along with the development of hypertensive disease: in the first stage in 40 per cent of the patients; in the second stage in 96 per cent, and in the third stage in 100%. Later on it was shown that similar relations also prevail in atherosclerosis: in the first stage of our classification, alterations are found in 82 per cent in the third stage in 93 per cent. Thus, ballistocardiography demonstrates a pattern common to both diseases: as they progress, there occurs a diminution of myocardial contractility.

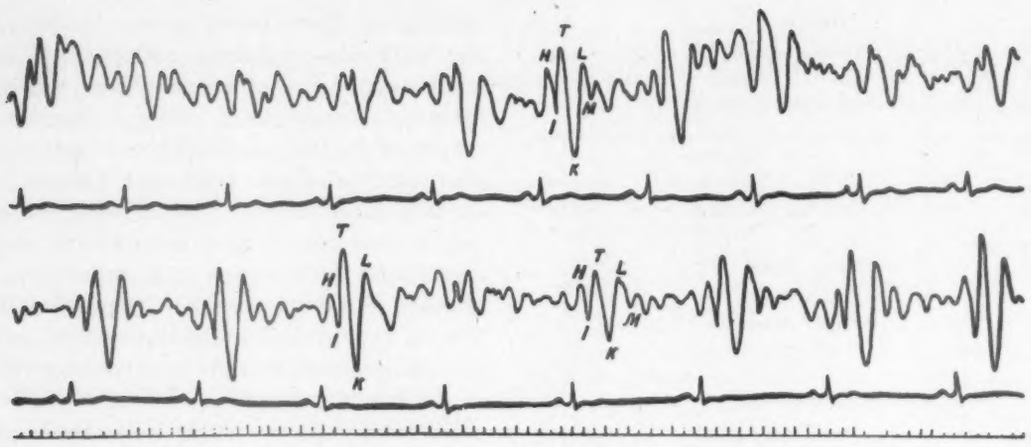

FIG. 4. Ballistocardiograms taken of a thirty-eight year old patient with hypertensive disease in the second stage. *Upper tracing*, changes of second degree according to Brown (fourth degree according to Lin Chen). *Lower tracing*, sixty minutes after injection of 0.5 mg. strophanthin, changes of the first degree.

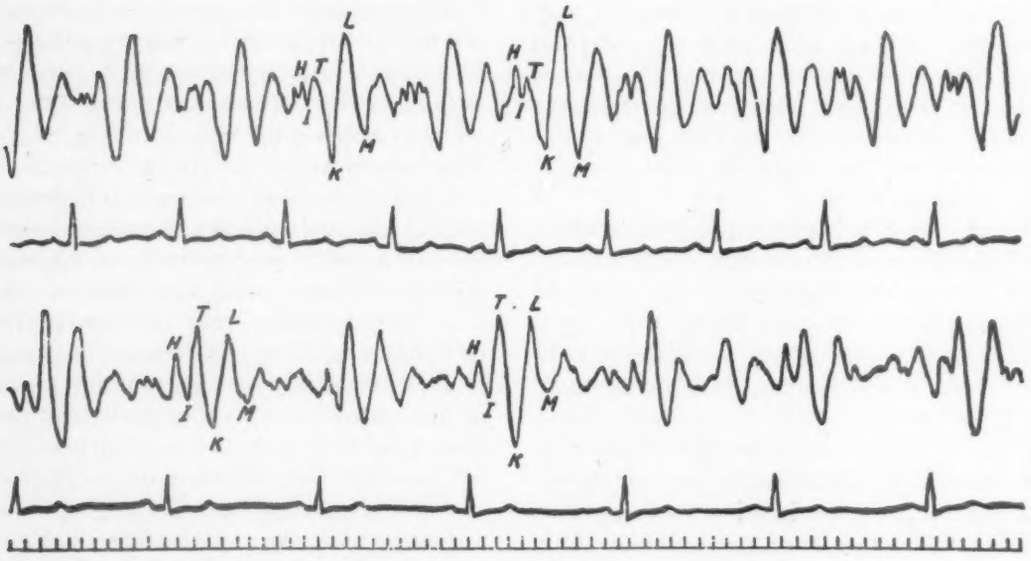

FIG. 5. Ballistocardiograms taken of a fifty-six year old patient with hypertensive disease in the third stage, coronary atherosclerosis, first stage, and angina pectoris. *Upper tracing*, changes of third degree according to Brown (fifth degree according to Lin Chen). *Lower tracing*, distinct improvement of the ballistocardiogram after injection of 0.5 mg. strophanthin.

The literature contains many statements to the effect that ballistocardiographic alterations depend mainly on the presence of coronary insufficiency. The analogous character of the ballistocardiographic alterations in cases of hypertension and atherosclerosis can possibly be explained on the grounds that a certain degree of coronary insufficiency exists in both conditions. It is worthy of note that the ballistocardiographic anomalies disappear after injection of strophanthin in the presence of hypertension as well as of atherosclerosis (Figs. 4 and 5). This militates in favor of a functional, reversible derangement underlying the disturbance of myocardial contractile activity In addition, the ballistocardiogram is improved under the influence of coronary dilating drugs in hypertensive patients as well as in those with atherosclerosis (Fig. 6). This, in turn, suggests that, in general, the ballistocardiographic alterations in both conditions are of vascular origin.

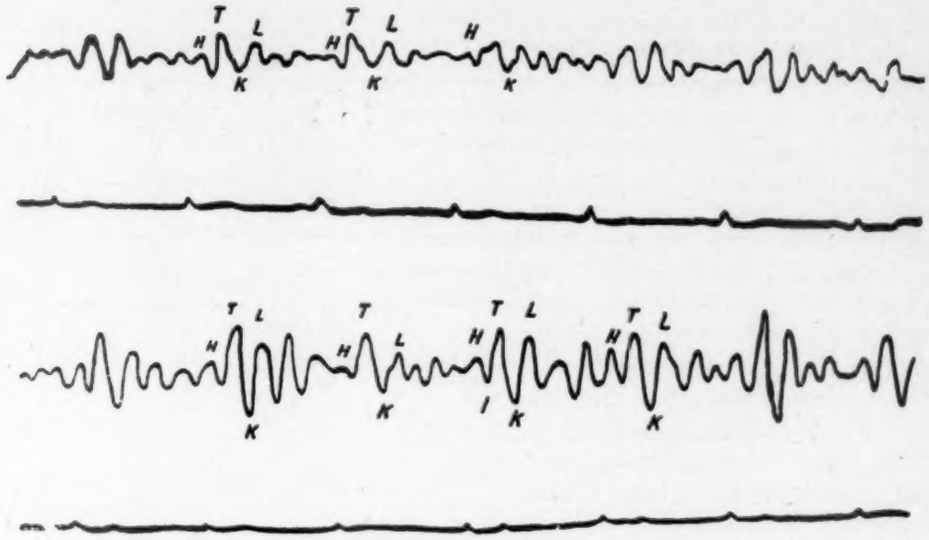

FIG. 6. Ballistocardiograms taken of a forty-eight year old patient with coronary atherosclerosis, first stage, and angina pectoris. *Upper tracing*, changes of second degree according to Brown (fourth degree according to Lin Chen). *Lower tracing*, distinct tendency toward normalization of the ballistocardiogram after administration of two drops of a 1 per cent solution of nitroglycerin; changes of the first degree.

AORTIC ATHEROSCLEROSIS IN HYPERTENSIVE DISEASE.

A fifth example of the complexity of the problem under consideration are the findings of *atherosclerotic changes of the aorta in hypertensive disease.*

Pulse Wave Velocity: Determination of the velocity of the pulse wave proved to be a valuable method, revealing different degrees of loss of elasticity of the aorta, as has been shown by M. J. Chvilivitskaya, A. F. Toor, co-workers of N. N. Savitsky, and also by our co-workers, L. K. Lokshina and U. T. Pushkar; in the presence of aortic sclerosis, the propagation of the pulse wave is accelerated. However, this phenomenon occurs also in hypertensive disease, although in a less pronounced form. We usually assume that in patients with hypertension in whom an acceleration of the aortic pulse wave is noticeable, atherosclerosis of the aorta probably also exists.

Furthermore, there is a relatively large group of patients with hypertensive disease in whom a comparison of the velocity of pulse wave propagation with that of young persons suggests a relative loss of aortic elasticity (Table III).

TABLE III

Comparison of Pulse Wave Velocity in Hypertensive Patients Without and With Atherosclerosis

Age Group (yr.)	Hypertension Without Atherosclerosis			Hypertension With Atherosclerosis		
	Total No.	No. of Patients with Pulse Wave Velocity:		Total No.	No. of Patients with Pulse Wave Velocity:	
		Normal (6.5–8.4 M./sec.)	Accelerated (8.5–11 M./sec.)		Normal (6.5–8.4 M./sec.)	Accelerated (8.5–25 M./sec.)
16–29	46	32	14	12	...	12
30–39	36	19	17	18	...	18
40–49	20	8	12	30	...	30
50–59	20	4	16	32	...	32

TABLE IV
Vascular Calcifications in Patients with Hypertension and Coronary Sclerosis

Age Group (yr.)	No. of Persons Examined	Calcifications		Localization			
		No.	%	Thoracic Aorta	Abdominal Aorta	Pelvic Arteries	Arteries of Legs
Hypertensive Disease							
30–39	40	1	2.5	...	1	...	...
40–49	263	60	22.8	3	36	22	13
50–59	369	159	43	19	112	80	46
60 and over	81	61	75.3	6	45	35	14
Total	753	281	37.3	28	194	137	73
Coronary Atherosclerosis							
30–39	2	...	...	...	...	...	...
40–49	44	15	34	1	6	3	9
50–59	108	54	50	6	41	16	12
60 and over	35	29	82.8	11	19	15	10
Total	189	98	51.8	18	66	34	31

Whether or not to assume in these patients the presence of atherosclerosis of the aorta remains a matter of arbitrary interpretation.

Roentgenographic Demonstration of Calcifications of the Aorta: This method serves as a useful means to detect atherosclerosis. According to data obtained by Z. G. Spektorova in the Institute of Therapy, it is possible, with a special technic, to identify exactly areas of calcification in the abdominal aorta and in the arteries of the pelvis and lower extremities. By thus systematically examining hypertensive patients, Z. G. Spektorova has found that in this disease, too, signs of calcification are present. In its third stage, calcifications were observed in 54 per cent, in the second stage in 32 per cent and in the first stage in 25 per cent of the patients. The frequent occurrence of calcifications in the third stage is not surprising because here it is easy to suspect a participation of atherosclerosis; however, the fact that calcifications are detectable also in the second and first stages of hypertensive disease makes one wonder, because calcification is undoubtedly a later manifestation of atherosclerosis. It appears that atherosclerotic changes with resulting calcifications in the abdominal aorta and in its ramifications develop frequently in the early stages of hypertensive disease. For comparison we can refer to reported calcifications of the same vessels in patients with coronary sclerosis, i.e., of myocardial infarction, without hypertension. The frequency of their occurrence depended on the age of the patients and, on the average, it exceeded only slightly the occurrence of calcifications in the third stage of hypertensive disease (Table IV). These comparisons compel us likewise to raise the question of interrelations between hypertensive disease and atherosclerosis.

NERVOUS FACTORS

It should be emphasized that the Soviet therapeutic school increasingly associates the etiology of both disorders with conditions of nervous strain. As regards hypertensive disease, this aspect of the question has been well explored by G. F. Lang. The problem of atherosclerosis, on the other hand, has not been subjected to extensive scientific investigation, even though C. P. Botkin and A. A. Ostroumov made statements concerning its neurogenic character. Yet, general medical experience speaks definitely in favor of a major significance

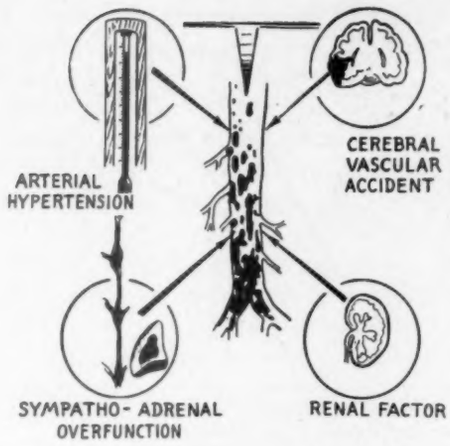

FIG. 7. Hypertension as a factor which both aggravates and mitigates atherosclerosis.

of disturbances in the nervous system as contributing to the development of atherosclerosis. For instance, indications of an increased nervous irritability, of neuropsychic overstimulation and overfatigue, and of acute or prolonged psychic trauma are encountered in the history of patients with myocardial infarction without hypertension as commonly as in that of patients with hypertensive disease without infarction. If nervous factors are regarded as significant in the etiology of hypertensive disease, there is probably no reason why they should not be considered in a similar sense also in that of coronary atherosclerosis.

Pathogenic Relationships Between Hypertension and Atherosclerosis

From the point of view of pathogenesis, the mutual relations between hypertensive disease and atherosclerosis are complicated. Both conditions can influence each other in an intensifying as well as in a mitigating sense.

Influences of Hypertension on Atherosclerosis

Increased Lipoidosis: Figure 7 demonstrates the influences exerted by hypertensive disease on the development of atherosclerosis. Undoubtedly, it can aggravate the latter. It is evident from the experimental investigations of K. G. Volkova and our co-worker B. S. Smolensky that an elevation of blood pressure markedly increases the lipoidosis of the vessels (in confirmation of the classic findings of N. N. Anitchkov). Possibly, an equally important role is played by tonic reactions of the arteries ("angiospasms") which alter the physicochemical condition of the arterial walls, particularly that of the coronary and cerebral arteries or of the vasa vasorum, thus predisposing them to an accelerated and more massive infiltration of cholesterol. There is also another factor that must not be overlooked. Hypertension is connected with an augmented sympathoadrenal activity and we know that the hormones of the adrenal medulla and, likewise, sympathetic impulses accentuate the development of experimental atherosclerosis. An intensification of experimental atherosclerosis under the influence of sympathomimetic drugs has been observed by our co-worker, J. K. Shkhvatsabaya.

Renal Factors in Hypertension: However, aside from these mechanisms, hypertensive disease can also inhibit the development of atherosclerosis under certain circumstances. One of these is renal insufficiency. Pathologists (P. P. Dvizhkov) have noticed that atherosclerosis is relatively uncommon and mild in malignant hypertension with renal arteriolonecrosis. This has even given rise to the erroneous concept of an antagonsim between hypertension and atherosclerosis. Experimental renal hypertension stimulates the development of cholesterol atherosclerosis less distinctly than, for example, hypertension due to coarctation of the aorta. It seems that in hypertensive renal disease certain factors supervene which weaken the inclination toward the atherogenic process.

Hypertensive Cerebrovascular Accident: The second example of an inhibitory influence of hypertension on coronary atherosclerosis is the hypertensive cerebral accident. It leads not infrequently to a cessation of vasomotor instability and reduces the tendency toward further coronary disturbances. It is worthy of note that after such an accident, hypercholesterolemia is sometimes diminished and attacks of angina pectoris and myocardial infarction occur more rarely.

Influence of Atherosclerosis on Hypertension

Let us now examine the influence which atherosclerosis may exert on hypertension (Fig. 8).

Renal Artery Atherosclerosis: Under certain conditions, atherosclerosis can intensify hypertension, depending mainly on its localization. Thus, atherosclerosis of the larger renal arteries, by inducing renal ischemia, may even cause a hypertensive state of the Goldblatt type. The

opponents of the neurogenic theory of hypertension are inclined to search for the cause in diseases of the kidney, and they especially emphasize the aforementioned fact all the more because the course of hypertension due to sclerosis of the large renal arteries is very similar to that of hypertensive disease in general. One must admit that in hypertensive patients such a localization of atherosclerosis (and even more so its localization in the abdominal aorta near the orifices of the renal arteries) is by no means uncommon, as our roentgenographic observations show.

Atherosclerosis of Carotid Sinus: Another mechanism which is apt to elicit hypertension in the presence of atherosclerosis consists of a derangement of the function of the depressor reflex apparatus located in the walls of the aorta and the carotid arteries (sinocarotid area). Under the influence of atherosclerotic changes in those vessels, there may occur a weakening of the vasodilator effects which are normally elicited by an augmentation of the cardiac stroke volume.

During the last several years, this neurogenic reflectory mechanism of hypertension has been extensively studied by the experimental school of Heymans, and also by N. N. Gorev, P. K. Anochin and others. Unquestionably, there exists the so-called aortic form of hypertension to which Lian has recently again called our attention.

Cerebral Atherosclerosis: A further localization of atherosclerosis which intensifies and perhaps even causes a tendency toward the development of hypertension seems to be the cerebral one. As is known from experiments of Iv. Navalishina and Taylor and Page, an experimental narrowing of the arteries which supply the brain elicits a prolonged elevation of the blood pressure. This cerebral ischemic hypertension is possibly the prototype of those hypertensive conditions that occur in the human being due to cerebral atherosclerosis. It is possible that an atherosclerotic interference with the nutrition of those cerebral areas which harbor the centers of the vasopressor system plays a major role in the development or stabilization of hypertension.

Cerebrovascular Disturbances: On the other hand, there are at least two ways by which atherosclerosis, on the contrary, may inhibit or even completely abolish hypertension. The first of these is the occurrence of cerebral hemorrhages and focal atherosclerotic injuries to the brain.

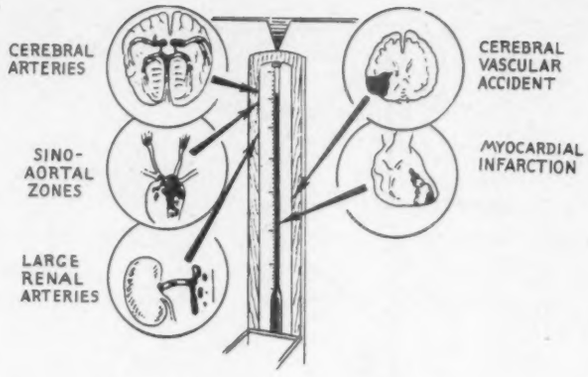

FIG. 8. Atherosclerosis as a factor which both aggravates and mitigates hypertension.

It has long been known that after a cerebral accident hypertension often subsides. It is astonishing how, in such instances, angiospasms disappear and a considerable improvement in the general condition of the patient takes place.

It has already been mentioned that atherosclerotic ischemia may, by itself, induce a reactive hypertension. From this it follows that atherosclerotic alterations of the cerebral circulation elicit either depressor or pressor effects, probably depending either on the location of the lesion or the intensity of the irritation.

Myocardial Infarction: The second vasodepressor mechanism in atherosclerosis is the occurrence of myocardial damage. Thus, as is generally well known, a lowering of the blood pressure is often seen after myocardial infarction, in cases of cardiac aneurysm and of myocardial fibrosis. This does not refer only to the so-called "decapitated" hypertension, i.e., to a reduction of the systolic pressure, while the high diastolic level is being maintained; rather both values drop in many instances to normal or even subnormal levels (i.e., the mean blood pressure is diminished).

A survey of the mutual influences of hypertension and atherosclerosis makes it clear, at any rate, that they do not develop in straight lines. Neither is it possible to declare categorically that hypertension aggravates atherosclerosis or that atherosclerosis aggravates hypertension, nor that atherosclerosis mitigates hypertension or that hypertension mitigates atherosclerosis. Both processes can influence each other in either direction, depending on the type, stage and localization of the pathologic changes. This must be taken into consideration in clinical practice.

Hypotheses on Nature of Relationship Between Hypertension and Atherosclerosis

Hypertension and Atherosclerosis Are Two Different Entities: According to customary interpretation, hypertensive disease and atherosclerosis appear as two separate independent diseases, as two nosologic entities. One of them, hypertension, is considered a nervous disorder, the other, atherosclerosis, an essentially metabolic one. The first would be purely functional (increased tonus of the vessels), the other would be characterized by conspicuous morphologic properties. The frequent coexistence of these two different disorders is caused by certain pathogenic factors which both have in common, including those discussed before: familial-hereditary predisposition, biochemical abnormalities, general circumstances inherent in living conditions, and nervous stress. The parallel development of both, in many instances, does not exclude their independent course in others. Both diseases modify each other. In practice we encounter both the "pure" forms of either one, and combined cases with prevalence of one or the other condition. In brief, they are two distinct but mutually interacting disorders, originating under closely related living conditions in a definite group of persons and, therefore, most commonly manifested simultaneously in such people.

Hypertension and Atherosclerosis Are Manifestations of One Disease: However, it is possible to express another point of view in consideration of the analogies of both conditions. In other words, hypertension and atherosclerosis are not separate diseases, but there rather exists only one single disease which manifests itself in some instances as hypertension, in others as atherosclerosis and, most frequently, as a combination of both pathologic processes, simultaneously or in succession.

The basic nature of this disease must reside in functional disturbances in the arterial system of central nervous origin.

One may postulate hypothetically that those disturbances consist of a neurosis, pathologically affecting vasomotor ("vasopressor") as well as trophic centers, i.e., centers which regulate metabolism (especially that of the lipids). It is possible that the primary and often intensive disturbance takes place in the function of the vasomotor centers (hence the early tendency toward pressor and vasodilator reactions, general and local), and that it causes hypertension as well as angiospasms (including those of the coronary and cerebral vessels, not infrequently also without hypertension).

In addition, there occurs a derangement of lipid metabolism, in some instances sooner, in others later.

We are now well acquainted with the fact that the brain plays an important, perhaps fundamental role in cholesterol metabolism. Thus, atherosclerosis appears as the result of centrally elicited vasomotor and metabolic influences. Of course, diet and an excessive alimentary consumption of fat and cholesterol influence the development of atherosclerotic changes. The more fat and cholesterol is consumed with food, the more will the central nervous apparatus for the regulation of lipid metabolism be put under strain, and the more reason will there be for a disturbance of its function. Consequently, under otherwise equal conditions, the alimentary factor turns the vascular disease in the direction toward atherosclerosis, so to speak. It intensifies and accelerates a more marked development of atherosclerotic vascular changes.

Thus, we have already begun to abandon the concept according to which the alimentary intake of cholesterol *per se* is regarded as the cause of atherosclerosis: it is now clear that atherosclerosis is not simply the result of an excessive dietary cholesterol intake, just as sugar diabetes is not a disease of those who eat candy.

The question arises as to why this basically single disease of the arterial system should occur in many instances with hypertension and without atherosclerosis or, on the other hand, with atherosclerosis without hypertension. We are reluctant to indulge in further speculations. One might argue that the difference could depend on the unequal timing and intensity of the disturbances in the respective centers, affecting in some patients chiefly the vasomotor center, in others the metabolic center.

In terms of the teachings of corticovisceral pathology, we suspect under certain conditions associated with a cortical neurosis a disturbance of the apparatus which regulates vascular function, as resulting in hypertension. Under other circumstances, we assume a derangement of the apparatus which regulates the function of the stomach to cause a peptic ulcer, etc. According to Selye ("Diseases of Adaptation") identical "stresses" produce in some instances vascular diseases, in others ulcers, rheumatism, etc. I cannot claim to be much impressed by all these theories—indeed, they leave gaping holes in

our understanding. Nevertheless, the "white areas" of science are gradually being narrowed down by the progress of new investigations.

The variations in the dynamics of the disease depend to an even greater measure on external circumstances: on the influences of the environment. We can understand that an excessive consumption of lipids will promote the development of the disease with respect to atherosclerotic changes, and that prevalence of acute emotional excitements will elicit vasopressor reactions. Finally, the previously discussed interactions of hypertension and atherosclerosis are bound to be of considerable importance as, for instance, an early involvement of the coronary system in the atherosclerotic process will inhibit the establishment of hypertension. In view of the aforementioned antagonistic influences upon the vascular processes, the functional condition of the central nervous system must be of particular significance in the origin of both syndromes.

In conclusion it should be said that I do not want to insist upon the views expressed here, but I felt that it might be useful to submit them for evaluation and criticism.

Summary

Arterial hypertension and atherosclerosis are often found in association. Hypertension is three times more frequent in association with atherosclerosis than alone in the same age groups.

There is much in common between hypertension and atherosclerosis as far as their hereditary-familial incidence is concerned. In family histories of hypertensive patients one often finds not only hypertension, but also atherosclerosis, and in family histories of atherosclerotic patients not only atherosclerosis, but also hypertension.

It is difficult to say when each of these morbid entities begins to develop; they rather develop simultaneously and in a parallel fashion. Biochemical differential diagnosis of both conditions is just as difficult, for changes in the lipids and the lipoproteins of the blood, characteristic of atherosclerosis, are encountered in arterial hypertension as well.

Nervous strain as an etiologic factor plays as great a role in hypertension as in atherosclerosis of the coronary arteries.

As to the pathogenic relationship of hypertension and atherosclerosis, it is not as simple and straightforward as is generally believed. Both processes may display intensifying and mitigating influences on each other.

It is possible to formulate two viewpoints on the nature of the relationship between hypertension on the one hand, and atherosclerosis on the other. The first implies that there exist two diseases of a different nature, which arise in closely related conditions of environment among persons of a definite type, and that they exert a mutual influence. The other viewpoint is that there exists but one basic disease which manifests itself as hypertension in certain cases, and as atherosclerosis in others; more often than not, both syndromes exist simultaneously or in succession.

Historical Milestones

Piorry on Percussion of the Heart

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SINCE THE advent of radiologic methods for measurement of cardiac size, the value of percussion of the heart has steadily diminished and is even considered by some[1] an obsolete procedure. Certain authorities,[2] however, suggest that some knowledge of percussion of the heart is desirable.

Credit for the invention of percussion belongs to Auenbrugger. His work was almost unknown until Corvisart translated it into French. Corvisart employed the method extensively in the diagnosis of cardiac disease.

Laennec, a pupil of Corvisart, invented auscultation of the chest and published his results in 1819. The observations of this man (who has been called "le maître observateur"[3]) on pulmonary sounds in health and disease, have passed through the years almost unchanged. His views on heart sounds and murmurs were, however, largely uncertain or even wrong. He misinterpreted the origin of heart sounds, assigning the first sound to contraction of the ventricles, and the second to contraction of the auricles. The significance of diastolic murmurs and pericardial friction rubs was not duly appreciated.[4]

In 1828, Piorry, a pupil of Laennec, reported an improvement of Auenbrugger's method of percussion. He utilized a pleximeter interposed between the percussing finger and the thoracic surface. The pleximeter itself was a small object made of ivory or wood. He described his observations in detail in a book entitled "De la Percussion Médiate." Its title was obviously inspired by Laennec's "De l'Auscultation Médiate." The accomplishments of Piorry were not first class, and he was far from attaining the brilliance of his predecessor. He exaggerated the clinical value of mediate percussion, and was involved in theoretic deductions that later brought discredit to the procedure.

Piorry, however, was one of the first nineteenth century authors to reintroduce percussion, and the first to advocate the interposition of a pleximeter. He was also the first to use one of the fingers of the left hand as a pleximeter. We must agree that Piorry had an uncritical mind, and his assertion that every organ had a special percussion sound is certainly fantastic.[5] He does not rank, of course, with men like Corvisart, Laennec or Bouillaud, but he wrote extensively and well about the heart.[4] The following translation must be considered with the knowledge that cardiac auscultation was not yet refined. It is taken from the 1831 edition of "Du Procédé Opératoire à Suivre dans L'Exploration des Organes par la Percussion Médiate."

* * *

PIORRY ON MEDIATE PERCUSSION OF THE HEART

How should one perform the cardiac study, by means of percussion, either on the living subject or on the corpse, before opening the chest?

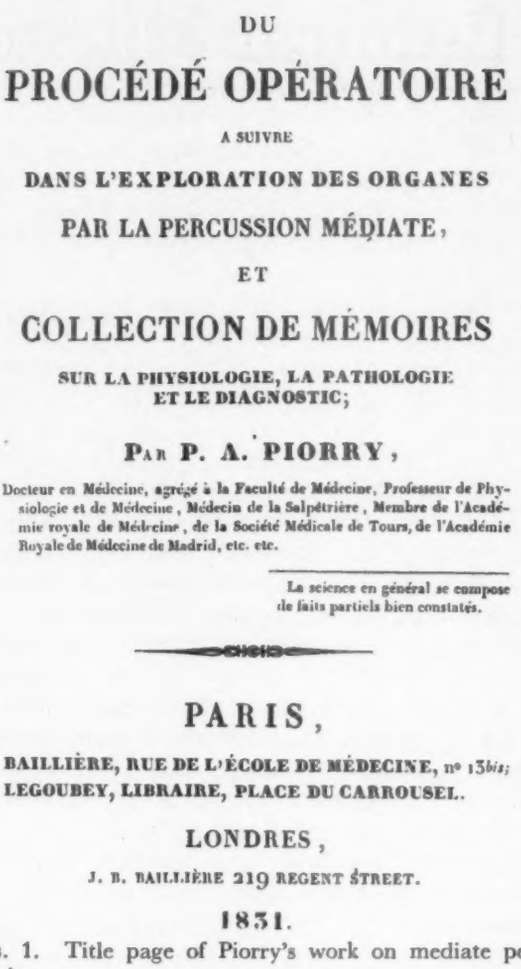
The patient and physician will be placed in front as for the examination of the chest. Once the clear sound of the upper sternum is recognized, the pleximeter will be successively lowered on the midline and anteriorly, just to the place where the sound begins to become unclear. The existence of this slight dullness will be confirmed by repeated strokes and the point at which it begins is marked with silver nitrate. Afterwards, we will perform percussion to the right, to recognize the superior border of the liver. This will be followed through the guide offered by the transitions of

dullness and clearness, which correspond to the points of contact of the lung and the uppermost portion of the superior aspect of the liver. It is necessary to perform percussion with a certain degree of energy, in order to correctly recognize the superior border of the liver, as it is deeply placed below the lung, that separates it from the chest wall.

Following the superior border of the liver, the pleximeter will be placed more and more to the left, until a duller sound is found. We will assure ourselves of the presence of this dullness through repeated strokes, marking the point with silver nitrate. This difference of sound occurs either at an inch to the right of the sternal border, more frequently on the border itself or actually on the midline. Once this sound is well noted, the instrument will be placed further to the left. A marked resistance to the percussing finger will be perceived and a greater degree of dullness will be heard: it is the left ventricle that gives these sensations. They are more marked when the left side of the heart is thickened, when its tissue is more solid and nearer to the costal walls. One or two inches to the left, a certain elasticity to the finger will be felt. These sensations will be obtained by means of a light percussive stroke, for if more energy is employed the dullness and resistance of the heart will still be perceived: it is here where the thin portion of the left lung begins. This point will be marked with silver nitrate. The pleximeter will be placed further to the left and dullness and resistance will progressively disappear, clearness and elasticity becoming more marked as the lung thickens. A point will be reached where either with a strong percussive stroke or with a very light one, a deep resonance and elasticity will be found. It is here that the lung alone fills the chest, and the heart will completely cease to correspond to the percussed points. These new limits will be marked with silver nitrate. . .

Once these precise notions of the cardiac circumference have been obtained, the left and posterior parts of the left hemithorax will be determined, to discover whether or not this organ is more than ordinarily developed in these directions.

. . . in pathologic conditions, the following alterations are found: in hydropericardium of considerable degree, dullness is present on the superior portion of the sternum, more than in both sides. We have observed right ventricular dilatation in a great number of patients at the



DU

PROCÉDÉ OPÉRATOIRE

A SUIVRE

DANS L'EXPLORATION DES ORGANES

PAR LA PERCUSSION MÉDIATE,

ET

COLLECTION DE MÉMOIRES

SUR LA PHYSIOLOGIE, LA PATHOLOGIE ET LE DIAGNOSTIC;

PAR P. A. PIORRY,

Docteur en Médecine, agrégé à la Faculté de Médecine, Professeur de Physiologie et de Médecine, Médecin de la Salpêtrière, Membre de l'Académie royale de Médecine, de la Société Médicale de Tours, de l'Académie Royale de Médecine de Madrid, etc. etc.

La science en général se compose de faits partiels bien constatés.

PARIS,

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1831.

FIG. 1. Title page of Piorry's work on mediate percussion.

Salpêtrière; a considerable extension (of one, two or three inches) and to the right of the midline of the region where the slight dullness was perceived. We have seen this space increase, becoming enormous when suffocation was impending, and then reduced when respiration became normal. The cases of this type presented to my observation are numerous, but from those that can be cited the most remarkable is the following: an old woman suffered extreme periodic attacks of suffocation. During the access, from one to two minutes, the cardiac area, particularly to the right of the sternum, increased two inches in extension. When respiration was free, dullness disappeared . . .

. . . left ventricular dilatation gives a remarkable dullness to the left of the cardiac region, to an extension corresponding to the degree of enlargement. It is sometimes of the order of five, six or seven inches. If hypertrophy is simultaneously present, the space occupied by the left ventricle does not exceed normal limits, but the resistance felt by the finger is extreme.

The dull sound, with little resistance, produced by right auricular dilatation, is found superiorly and to the right of the cardiac region, while in hydropericardium, it is mostly upward that dullness is recognized. I have not observed during life the results that percussion should give in patients with left auricular dilatation.

All the cardiac chambers, but particularly the right, vary infinitely in volume: (1) in alterations of the quantity of blood of the subject: they are dilated in states of plethora, reduced in anemia; (2) in disturbances of the pulmonary circulation, the blood accumulates in the right cardiac cavities; and (3) in stenosis of the cardiac orifices, and it is below the obstacle that the fluid dilates the organ.

. . . the heart diminishes in volume in a remarkable manner after blood letting, sometimes several inches.

. . . combining the aforementioned signs with those furnished by the pleximeter in diseases of the lung and pleura, we can distinguish the coexistence of several of these lesions. Left-sided hydrothorax, even if voluminous, will not render difficult the recognition of involvement of the heart.

. . . it is by taking into account the displacement of the fluid, by the changes of the patient's position and placing him in a position in which liquid is removed as far as possible from the heart, that we come to recognize the double lesion we are investigating. Thus, in a similar instance, the patient will be reclined on his back, and inclined in the right lateral decubitus position. In this position, only abundant effusions will render the measurement of the heart difficult.

. . . the hypertrophied thymus, or a tumor, can be located at the superior sternal portion, and make one believe that the right auricle or the pericardium extend to that region. But these instances are quite rare, and moreover, some clear points between the dullness of the heart and that of the tumor will be found sufficient to distinguish these diverse parts. Recently, I think I observed an aneurysm of the thoracic aorta. It was developed superiorly and to the left of the sternum. Simple pulsations were felt, and dullness was present to an extension of two by three inches. Below the tumor, between it and the heart, a manifest clearness was found. I have lost sight of this patient, who presented the general and pleximetric signs of considerable hypertrophy of the left ventricle. Lesèble has recently communicated to me an observation in which an aneurysm of the aorta was recognized and its limits defined by pleximetric percussion of the tumor. Necropsy completely verified the diagnosis made during life.

From these considerations it is evident that pleximetric exploration is of great usefulness in the diagnosis of heart disease. Direct percussion, in the hands of Corvisart, already had immense advantages, and some of his pupils derived important results through its means. I have frequently compared it to pleximetric percussion, and I do not hesitate to affirm that it is far from having the accuracy and certitude of this last method.

. . . we can deduce many therapeutic points from the exact appreciation of the variations induced in cardiac volume by blood letting, from the almost certain diagnosis of hemopericardium, from the positive distinction established by the pleximeter between dilatation and hypertrophy, from the knowledge of the coexistence of pleural effusion. . . .

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Letter to the Editor

Cerebral Air Embolism During Left Heart Catheterization

Dear Sir:

I would like to call your attention to an unusual occurrence which has been witnessed by Dr. Lekos and myself at the Hippokration Hospital in Athens.

Air embolism into the venous system is not a rare phenomenon. It may occur as a complication of surgical operations or wounds of the neck or chest, by way of the uterine veins in a case of placenta previa or after washing of the maxillary sinus. The results of venous embolism are usually not serious because the amount of air required for causing symptoms is great and the rate of infusion must be rapid. An exception is represented by cases of atrial septal defect, when a paradoxical embolism takes place. Caisson disease is another condition where air embolism is reponsible for serious complications or death.

Contrary to venous embolism, *air embolism into the left side of the heart or the aorta* is dangerous and its consequences are usually fatal. Smaller quantities of air are required to cause serious symptoms or death when injected into the systemic circulation because they may occlude arterioles or capillaries of the brain. Systemic air embolism can occur after injuries to the chest, during artificial pneumothorax, pleuropulmonary operations or neurosurgical procedures in the sitting position. More recently, with open heart surgery, the danger of air embolism has become greater.

The possibility of air embolism during left heart catheterization is known, but this occurrence is extremely rare. Recently we had the opportunity to observe such a case during a retrograde catheterization of the left side of the heart through the aorta. It may be useful to report briefly on this case in order to bring attention to the consequences of such a procedure.

Case Report: A. P., a forty-four year old man with aortic insufficiency entered the Cardiac Ward for an evaluation of his condition for possible corrective surgery. Retrograde catheterization of the left heart was attempted through the right brachial artery. Instead of entering the ascending aorta, the catheter entered the right carotid artery, as may occur during this procedure. A slow infusion of normal saline was given under pressure in order to prevent blood clotting. During the manipulation of the catheter, the perfusion bottle became empty and, in a few seconds, a considerable amount of air entered the carotid artery under significant pressure. The connection with the bottle was interrupted and the catheter was immediately withdrawn. However, the patient stopped breathing, became pale and convulsive seizures started. His heart beat remained regular.

The patient was placed in the Trendelenburg position in order to speed absorption of the air. Artificial respiration was started and oxygen was administered under pressure. After a few seconds, the patient was breathing irregularly with a Cheyne-Stokes type of respiration. He had mental confusion with complete disorientation and hallucinations, followed by new convulsive seizures and vomiting. His pupils became dilated and reacted poorly to light and accommodation. Phenobarbital and Thorazine® were given. After a half hour, the convulsions stopped, but the patient remained confused and disoriented. The heart beat and blood pressure remained normal. A neurological examination showed a positive Babinski reflex in the left foot and increased reflexes in all extremities. Liebermeister's sign was negative. A fundoscopic examination showed low arterial pressure of the retinal arteries with greatly diminished arterial pulsations. The electrocardiogram remained unchanged. Convulsions started again and subsided only after use of intravenous Pentothal.® With periods of improvement and deterioration, the patient remained in about the same condition for the next twenty-four hours, under constant sedation with phenobarbital and Thorazine. The next day he felt better, and the convulsions had subsided, but he was still disoriented from time to time and was unable to see. The third day he was completely relaxed and able to answer questions, but remained blind. Finally, on the fourth day, his vision reappeared and the neurological symptoms disappeared. At the end of the first week, he had completely recovered, and showed no neurological signs.

This case proves that accidental air embolism to the brain is not invariably fatal.

CHRIST ARAVANIS, M.D.
Hippokration Hospital
Athens, Greece

Abstracts

American College of Cardiology, Ninth Annual Convention*

DIAGNOSIS AND TREATMENT OF CARDIAC TUMORS. *Crawford W. Adams, M.D., F.A.C.C., Harold A. Collins, M.D.* and *Joseph H. Allen, M.D.* Vanderbilt University School of Medicine, Nashville, Tenn.

Myxoma of the atrium is a relatively infrequent lesion which assumed clinical importance with the introduction of successful methods for intracardiac surgery. Recent reports attest to the increasing frequency of accurate preoperative diagnosis and successful removal of these tumors.

The usual clinical manifestations arise from obturation of the mitral or tricuspid value. Our experience with two unusual cases of atrial myxoma is presented in an attempt to further elucidate the characteristics, diagnostic methods and surgical treatment of this lesion.

Myxoma of the right atrium was suspected clinically and confirmed by angiocardiography in one patient. The tumor arose within the right atrium and prolapsed through the tricuspid valve into the right ventricular cavity. Using the temporary cardiopulmonary bypass the tumor was successfully removed. However, death due to preceding hepatic, adrenal and myocardial insufficiency occurred on the third postoperative day. In a second patient with a left atrial myxoma, death occurred from embolization of tumor fragments into the superior mesenteric artery.

The electrocardiographic, phonocardiographic and roentgenographic characteristics in these patients are considered in detail and the surgical technics available for removal of such tumors are discussed.

ESTIMATION OF STATE OF PERIPHERAL ARTERIAL TREE FROM ELECTRONIC PULSE WAVE STUDIES. *Joe Armbruster, M.D.* Indiana University Medical Center, Indianapolis, Ind.

By measuring pulse waves at various levels in the limb, surprisingly good estimation of the state of the arterial tree is possible. Such estimations are compared with arteriographic studies.

ELECTROCARDIOGRAPHIC CHANGES FOLLOWING THE ADMINISTRATION OF THYROID STIMULATING HORMONE. *Saul P. Baker, M.D., Ph.D., Milton Landowne, M.D. and George W. Gaffney, M.D.* Gerontology Branch, National Heart Institute, National Institutes of Health, Bethesda, Maryland, and the Baltimore City Hospitals, Baltimore, Maryland.

Thyroid stimulating hormone (thyrotropin; TSH) was administered intramuscularly in daily doses of 25 mg. (10 U.S.P. units) to five euthyroid men, aged forty-six to ninety-two years, on each of four or five successive days. Four of the five subjects demonstrated definite electrocardiographic abnormalities during and immediately following the period of administration. These abnormalities included premature atrial and ventricular systoles, S-T depression and diminution and inversion of precordial T waves. This evidence of change in myocardial irritability and repolarization appeared and declined *early* in relation to change in heart rate and basal metabolic rate. Sedimentation rate did not change, and serum glutamic oxalacetic transaminase, assayed in four subjects, did not become abnormal.

The nature and time course of these changes may provide information on the mechanism of thyroid stimulation of the heart, and are compatible with an hypothesis that thyroidal effects on the heart are, at least in part, mediated by a sympathomimetic mechanism. Other explanations, however, are not excluded. These observations are of clinical interest and suggest a test of this hypothesis in man.

A COMPARISON OF PULMONARY HEMODYNAMICS WHEN DETERMINED AT TIMED INTERVALS DURING EXERCISE IN PATIENTS WITH PULMONARY EMPHYSEMA AND HYPERTENSION. *Roy H. Behnke, M.D., Douglas H. White, M.D. and John F. Williams, Jr., M.D.* V. A. Hospital and Indiana University School of Medicine, Indianapolis, Ind.

The pulmonary artery pressure during graded steady state exercise in the normal subject in the supine position initially rises slightly. After six to seven minutes there may be a fall to a level below the control resting value. It is also reported that the cardiac output in normal subjects attains a constant level after two minutes of graded exercise and that the pulmonary vascular resistance falls. Such changes may obviously lead to misinterpretation of data when attempting to evaluate the action of drugs on the pulmonary vascular bed during exercise.

In order to determine the effect of prolonged exercise on a restricted pulmonary vascular bed, five patients with pulmonary emphysema who were free of congestive heart failure were studied in the supine position by right heart catheterization with determination of pulmonary artery and capillary pressures and cardiac outputs at rest and intermittently during steady state exercise. During exercise, the cardiac output was determined

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between two to three, four to five, six to seven and eight to nine minutes, and the pulmonary artery pressures at the termination of each output. Capillary pressures were recorded at rest and after nine minutes of exercise.

Four patients had resting pulmonary hypertension, and all had normal resting cardiac outputs and capillary wedge pressure. During exercise all demonstrated abnormal pulmonary artery pressures. The pulmonary artery pressure reached its maximum value in four patients at the end of five minutes and in the fifth patient at the end of three minutes of exercise. Thereafter the pressure decreased by 4 mm. Hg in one patient, 3 mm. Hg in another, 1 mm. Hg in two and 0 in one. In no patient did the values return to control levels.

The cardiac output reached a constant level between the second and third minute in four patients and between the fourth and fifth minute in the other. After the attainment of a steady state, the greatest variation in output during these periods was 904 cc./minute. The pulmonary vascular resistance was constant during exercise with only one patient showing a significant decrease, this of only 68 dynes. All capillary pressures were normal at the termination of exercise.

It is believed that a steady state in hemodynamics may be attained at the end of five minutes of exercise. The pulmonary artery pressure, vascular resistance and cardiac output do not decrease significantly with prolonged exercise in patients with pulmonary emphysema and hypertension.

THE ELECTROCARDIOGRAM IN ACUTE AND CHRONIC COR PULMONALE. *Michael Bernreiter, M.D., F.A.C.C.* Kansas City, Mo.

The electrocardiographic pattern of acute cor pulmonale is most commonly caused by pulmonary embolism. The changes are transient and variable. Tracings obtained soon after the acute episode and followed by serial electrocardiograms are most important for correct diagnosis. Typical findings can be divided into the following categories: (1) There is a shift of the electrical axis to the right. Prominent S waves may appear in lead I and dominant Q waves in lead III. The S-T segment is depressed in lead I and elevated in lead III. The T wave is typically upright in lead I and inverted in lead III. This pattern could be mistaken for posterior myocardial infarction except that aVF does not show the typical Q wave found usually in posterior infarction. It should also be remembered that the electrocardiographic changes brought about by pulmonary embolism disappear usually in one to two weeks. (2) Transient right bundle branch block. (3) Clockwise rotation of the heart around the longitudinal axis, with a shift of the transitional zone to the left. This is the result of pulmonary hypertension. (4) Transient cardiac arrhythmias (auricular flutter, auricular fibrillation, paroxysmal auricular tachycardia).

Chronic cor pulmonale is usually due to pulmonary emphysema, extensive pulmonary fibrosis, chest deformities, mitral stenosis and congenital cardiac lesions. The electrocardiogram exhibits permanent changes consisting of right axis deviation, right ventricular hypertrophy, P wave changes and complete and incomplete right bundle branch block.

CARDIOGENIC SHOCK: TREATMENT WITH A NON-VASOCONSTRICTOR PRESSOR AMINE. *Arthur Bernstein, M.D., F.A.C.C.* Newark Beth Israel Hospital, Newark, N. J.

Based upon new studies, mephentermine sulphate was given intravenously to patients in cardiogenic shock in doses of 60 mg. at one time, followed by a continuous intravenous drip of 600 mg. of mephentermine in 500 cc. of 5 per cent glucose in distilled water. The criteria for the presence of shock were (1) systolic pressure less than 80 mm. Hg, (2) tachycardia, (3) diaphoresis, (4) anxiety, (5) peripheral vasoconstriction with cool, clammy skin and (6) air hunger. In a series of sixty such patients, doses from 60 to 3,000 mg. in seventy-two hours were given with no untoward side effects. In forty-five of the sixty patients (75 per cent), there was an effective rise in blood pressure; ten patients had a poor to fair response and five failed to respond. The ultimate survival rate of the entire group was 34 per cent. This compares with a 5 per cent survival rate before the use of vasopressors at our hospital.

In summary, mephentermine has the physiologic advantages of being an inotropic, vasodilating, antiarrhythmic vasopressor amine theoretically ideal and clinically proved to be effective for the treatment of cardiogenic shock. For the clinician it has further value because it can be given either intravenously or intramuscularly by syringe in one 60 mg. dose without danger of slough or undue rise in blood pressure. It can also be given by drip without local slough or fear that slight variations in the rate of administration will result in marked changes in blood pressure levels.

THE IMMEDIATE EFFECT OF MITRAL COMMISSUROTOMY ON PULMONARY COMPLIANCE. *Stuart Bondurant, M.D., Robert King, M.D.* and *Harris B. Shumacker, M.D.*, Indiana University Medical Center, Indianapolis, Ind.

Pulmonary compliance is usually reduced (lungs stiffened) in patients with mitral stenosis, and dyspnea has been attributed to this change. The importance of pulmonary vascular hypertension and engorgement in causing decreased compliance has not been established. To study the compliance change associated with an acute decrease in pulmonary vascular pressures, compliance has been measured at operation within five minutes before and after mitral commissurotomy. Eight subjects, aged sixteen to thirty-four, with mitral valve areas of 0.6 to 1 sq. cm. no significant mitral insufficiency and postcommissurotomy mitral valve areas of 2 to 3 sq. cm. (surgeon's estimates), were studied. Pulmonary artery pressures, and in three cases left atrial pressures, were measured directly before and after commissurotomy. Because of the thoracotomy, transpulmonary pressure was represented by the difference between airway and atmospheric pressures. While this technic has been validated in thoracotomized animals, application to man must be made with reservation because of the intact mediastinal septum. The absolute value obtained for pulmonary compliance may not be valid but changes in compliance should be accurately reflected. Tidal volume was measured with a wire screen flowmeter. Measurements were made just before and after commissurotomy when the level of anesthesia, systemic arterial pressure, heart rate, respiratory rate and tidal volume were comparable.

These are the results: Pulmonary artery pressure

decreased from 72/29 to 60/22 mm. Hg (group mean); left atrial pressure (three patients), from 38/22 to 20/9; and pulmonary compliance increased from 0.053 to 0.062 L./cm. water. The change in compliance was of variable magnitude, not correlated with the magnitude of the change in pulmonary artery pressure and, for the group, was not statistically significant. However, two subjects who manifested increases in compliance (decreased lung stiffness) of 50 and 100 per cent were among those with the most marked decrease in pulmonary artery pressure. It is concluded that changes in pulmonary vascular pressure of the magnitude which followed mitral commissurotomy in these patients do not consistently alter pulmonary compliance.

RENAL AUTOREGULATION. *Gustavo Bounous, M.D.* and *Harris B. Shumacker, M.D.* Indiana University Medical Center, Indianapolis, Ind.

Relative renal autoregulation is confirmed by direct measurement of renal flow in normal dogs, in animals in which renal flow is increased by the intravenous administration of dextrose and in animals made acutely hypovolemic. Autoregulation is abolished by renal decapsulation.

THE NORMAL QRS VECTORCARDIOGRAM IN INFANTS AND CHILDREN FROM BIRTH TO FIFTEEN YEARS. *Homobono B. Calleja, M.D., Raymond E. Barker, M.D.* and *Ray W. Kissane, M.D., F.A.C.C.* White Cross Hospital, and the Ohio State University College of Medicine, Columbus, Ohio.

Previous studies on the normal vectorcardiograms of infants and children have been limited to specific age groups. This study included the period of infancy and childhood from birth to fifteen years, inclusive.

Using an apparatus similar to that of Shillingford and Brigden and employing the cube system of Grishman, 166 QRS vectorcardiograms of 154 patients with normal hearts were taken and analyzed according to morphology and rotation of the loop and position of the 0.02, 0.03, 0.04 and 0.05 second instantaneous vectors. The age of the patients ranged from birth to fifteen years, inclusive. Six patients were followed up with serial vectorcardiograms through their "transition" period. The horizontal plane was found to be most informative in following the progression of the loop from birth to fifteen years.

The progression of the loop was conveniently divided into three age groups. Group 1 consisted of infants aged from birth to one month. The QRS loop in this group showed considerable variation with transition forms beginning as early as the first three days of life. The 0.02 and 0.03 second vectors were directed anteriorly, either to the right or to the left. The 0.04 second vector was widely scattered, while the 0.05 second vector was near or at the E point. Group 2 included patients aged from one month to one year. Figure of eight patterns were common. Group 3, patients aged from one year to fifteen years, showed all counterclockwise rotation in the horizontal plane. Some figure of eight patterns were seen up to ten years but none later. Normal adult pattern was seen from ten to fifteen years. The 0.02 and 0.03 second vectors were directed to the left and anteriorly, while the 0.04 and 0.05 second vectors were directed to the left and posteriorly.

THE CURRENT STATUS OF BILE ACID METABOLISM WITH PARTICULAR REFERENCE TO CHOLESTEROL. *Robert B. Failey, Jr., M.D.* Indiana University School of Medicine, Indianapolis, Ind.

The bile acids are presently considered the final oxidation product of cholesterol and as such represent an important means for the excretion of cholesterol. Analysis for its bile acid content of gallbladder bile obtained at autopsy showed variability in composition with changes in the degree of atherosclerosis. Specifically, the ratio of dihydroxycholanic to trihydroxycholanic acid rose as atherosclerosis increased. Further study of this correlation was suggested in particular because deoxycholic acid, an important component of the dihydroxy group, has been shown to be a product of bacterial action in the intestine. Antibiotic therapy appropriate to alter the bile acid content of the intestinal contents has been followed by lowering of the serum cholesterol in man and animals. Since feeding of diets rich in linoleic acid also lowers the ratio of dihydroxy- to trihydroxycholanic acid, an important, although presently unexplained, correlation may be involved in this aspect of cholesterol metabolism.

As they are excreted into the bile, bile acids are conjugated with either of the amino acids, glycine and taurine. Taurine, an organic sulfur compound, is of particular interest because it is the predominant conjugate found in animals low in the evolutionary scale. Among the various species of animals surveyed, there appears to be a rough correlation between "immunity" to atherosclerosis and the percentage of taurine conjugation of bile acids. Preliminary studies have shown that nicotinic acid, used as an agent to lower serum cholesterol levels in man, enhances taurine conjugation. The significance of this and other aspects of bile acid metabolism are under current investigation with particular reference to their relationship to cholesterol metabolism.

HIGH SERUM TRANSAMINASE LEVELS FOLLOWING MYOCARDIAL INFARCTION WITH RECOVERY. *Maxwell L. Gelfand, M.D., F.A.C.C.* and *Robert Fishbein, M.D.* New York, N. Y.

Recently we have observed eight patients with myocardial infarction and serum transaminase levels ranging from over 500 to 1,800 units, who recovered. In the one patient with marked elevation who subsequently died, autopsy revealed an underlying pancreatic carcinoma with metastases to the liver. Furthermore, all the electrocardiograms of this group were analyzed and found to be as extensively involved as was to have been expected from the rise in the serum transaminase level.

The purpose of this paper is to present these cases and to emphasize that although SGOT levels are extremely useful in indicating the degree of myocardial necrosis, marked elevations are not necessarily incompatible with recovery. When serum levels rise following a previously noted decline, however, this may indicate not only extension of the original infarction but also possible hepatic involvement, either primary or secondary. We are likewise convinced that the changes in the electrocardiogram are proportional to the elevated serum transaminase level.

EFFECT OF POTASSIUM AND DIGITALIS ON VENTRICULAR ARRHYTHMIAS AND A-V CONDUCTION: A REAPPRAISAL OF DIGITALIS AND POTASSIUM RELATIONSHIP. *Charles Fish, M.D., B. L. Martz, M.D.* and *Fred H. Priebe, M.D.* Marion County General Hospital, and Indiana University School of Medicine, Indianapolis, Ind.

The present study was designed to re-evaluate the relationship of potassium and digitalis at the (1) arrhythmia and (2) A-V conduction levels.

(1) Ventricular arrhythmia was produced in dogs with acetyl strophanthidin and at that point an injection of isotonic potassium phosphate (155 mEq./L.) was given at a rate of 1 to 1.2 mEq./minute. When the arrhythmia was abolished the infusion was terminated and the duration of the S-A rhythm and the recurrent arrhythmia were carefully observed.

The acetyl strophanthidin-induced ventricular arrhythmia was abolished uniformly by the administration of potassium in amounts varying from 2.1 to 6 mEq./L. with an average of 3.9 mEq./L. However, within a half to two minutes after the infusion was discontinued the ventricular arrhythmia reappeared. The plasma potassium at the time the arrhythmia was abolished varied from 5.6 to 6.9 with an average of 6.4 mEq./L. The potassium level when the arrhythmias recurred varied from 5.3 to 5.7 with an average of 5.5 mEq./L. The control potassium in dogs submitted to this study varied from 3.5 to 3.9 mEq./L. with an average of 3.8 mEq./L.

(2) Second degree A-V block was produced by infusion of potassium phosphate. The animals were then given 0.5 mg./kg. (not to exceed 5 mg.) of digitoxin intramuscularly. Forty-eight hours later the potassium was again infused to second degree block. Prior to administration of digitoxin 12.7 to 26.3 (average 18.3) mEq. of potassium was necessary to induce second degree block. After digitoxin was given, second degree block appeared after the infusion of 4.8 to 9.7 (average 5.8) mEq. of potassium.

Our studies indicate that (1) the depression of ventricular arrhythmia by potassium is transient and probably related to levels of extracellular potassium and (2) that the A-V conduction system is more sensitive to the depressing effects of potassium after intoxication with digitoxin. The results do not confirm the existence of a specific digitalis and potassium antagonism.

THE MEDICAL TREATMENT OF CORONARY INSUFFICIENCY. NEW DRUGS AND NEW METHODS OF EVALUATION. *Rudolph Fremont, M.D., F.A.C.C.* V. A. Hospital, Brooklyn, N. Y.

Nitroglycerine, which was discovered in 1860, is still considered by most physicians the only truly reliable means of relieving attacks of angina pectoris. Recently developed methods of objective drug evaluation have led to the discarding of a host of drugs heretofore claimed to have a coronary dilatory effect. The persistent need for a nitroglycerine-like medication of prolonged activity has led, however, to the search and discovery of two new groups of drugs. One consists of nitrates of a new type (sorbide dinitrate) or in a new form of administration (sublingual erythroltetranitrate) which may influence coronary blood flow directly. The other group is made up of monoamine oxidase (MAO) inhibitors which may modify the perception of pain in general or influence myocardial oxygenation by interaction with norepinephrine and related compounds.

This report is based on personal observations of thirty ambulatory patients with a typical anginal syndrome most of whom had sustained a well documented attack of myocardial infarction or had an abnormal exercise electrocardiogram. Their response to both types of antianginal drugs was evaluated over a period of at least two years.

Both subjective and objective response analyses were carried out. The first included the use of daily report cards listing the amount of effort causing anginal attacks, the frequency of rest pain and the amount of nitroglycerine used in either instance.

In addition, closely matching placebo therapy was employed in the nitrate study and a double blind technic in that of MAO inhibitors. Serial ballistocardiograms at rest and frequently also after smoking were obtained on all patients. Serial exercise electrocardiograms were obtained when considered safe.

The results of these observations in terms of drug response and tolerance, and as correlated with all factors known to affect the natural course of coronary disease are discussed in detail. The over-all advantage of nitrate therapy in coronary insufficiency as noted with erythroltetranitrate and sorbide dinitrate over that of MAO inhibition is demonstrated with the help of representative cases. The particular methods of observation are discussed in detail and the pitfalls occurring even with the most objective methods are demonstrated.

AN INVESTIGATION OF THE VASODEPRESSOR RESPONSE TO GANGLIONIC STIMULATING DOSES OF ACETYLCHOLINE. *R. W. Gardier M.D., P. C. Johnson, M.D., R. P. Roesch, M.D.* and *V. K. Stoelting, M.D., with the technical assistance of S. L. Graham.* Indiana University School of Medicine, Indianapolis, Ind.

Previous studies have shown that an alkyl substituted urea compound, N,N diisopropyl, N isoamyl diethylamino ethyl urea (P-286) is capable of reversing the pressor effect of large intravenous doses (1 mg./kg.) of acetylcholine in the atropinized dog. It has been determined further that this vasodepression results from specific blockade of adrenal medullary discharge. This study was undertaken to elucidate the mechanism responsible for the acetylcholine blood pressure fall.

The reversal is not affected by dichloroisoproterenol given in doses adequate to prevent an isoproterenol vasodepression of similar magnitude. In addition, animals treated with reserpine, sufficient to expect a depletion of peripheral catecholamine stores, still demonstrate the reversal.

Since other workers have shown that P-286 can decrease the catecholamine content of the heart and other visceral organs, the vascular action of acetylcholine was studied on an isolated segment of dog ileum *in situ*. P-286 has a transient vasodepressor action *per se* which presently appears to be due to a decrease in vascular resistance. This vasodilation is more prominent in the innervated versus the denervated preparation, and most likely results from the weak ganglionic blocking action previously shown for this compound.

Regarding the mechanism of acetylcholine reversal, the following has been noted. Prior to P-286, marked vasoconstriction (85 per cent of cases) accompanied the acetylcholine pressor effect. After P-286 the resistance changes following acetylcholine could not be unequivocally implicated for the depressor effect noted. Further studies are needed to determine whether the fall in blood

pressure is cardiac in origin. This is of special interest because P-286 has been shown to have antiarrhythmic properties.

EXPERIENCES IN CINEFLUOROGRAPHY. *Robert S. Green, M.D., F.A.C.C.* St. Mary's Hospital, Cincinnati, Ohio.

Cinefluorography represents a relatively new field of medical investigation that will become increasingly important. This presentation outlines the problems that have occurred during four years' experience with the development of this technic. Our cinefluorographic apparatus allows us to obtain from $3^3/_4$ to 30, 35 mm. motion pictures per second of an 8 by 8 to 14.5 by 14.5 inch fluoroscopic screen area with relatively low patient radiation.

The discussion covers technical aspects of producing films, patient and personnel radiation, as well as film analysis. In relation to the latter we have developed a 35 mm. analyzer that enables us to study films frame by frame, forward or backwards, or at any motion speed up to 24 frames per second. Films are shown without flicker at frame speeds as low as 6 per second. Films are available for analysis within one hour of any procedure. A comparison of this method of cinefluorography with image intensification is included in the discussion.

CINEANGIOCARDIOGRAPHY. *Robert S. Green, M.D., F.A.C.C., Fernando L. Mendez, M.D., Erna L. Borousch, M.D., Paul G. Geiss, M.D., Muzafer Aytur, M.D.* and *Gerhardt G. Hilt, M.D.* St. Mary's Hospital, Cincinnati, Ohio.

This presentation details the technics and results with various types of cineangiocardiograms, i.e., single and double venous, selective, left ventricular and retrograde brachial. Emphasis is placed on the value of the relatively simple technic of retrograde brachial cineaortography in the diagnosis of patent ductus arteriosus.

Excellent opacification of the pulmonary arteries from the dye-filled aorta plus early filling of the left auricle has been demonstrated in five infants from seventeen days to nine months of age in whom precise evaluation was mandatory because of impending failure. Similar results have been obtained on older children and adults. All cases have been verified by surgery.

CINEFLUOROGRAMS OF THE BARIUM SWALLOW AND OF HILAR ACTIVITY. *Robert S. Green, M.D., F.A.C.C., Fernando L. Mendez, M.D., Erna L. Borousch, M.D., Paul G. Geiss, M.D., Muzafer Aytur, M.D.* and *Gerhardt G. Hilt, M.D.* St. Mary's Hospital, Cincinnati, Ohio.

The presentation includes full chest motion picture films of normal and abnormal barium swallows and of varying degrees of hilar activity. These results are correlated with findings from other procedures such as cardiac catheterization.

The average skin radiation for each patient sequence was 1.5 r. This contrasts favorably with the 10 r figure reported with one minute of routine chest fluoroscopy. The value of motion picture records for group analysis, teaching and subsequent comparative studies is discussed.

RESTENOSIS AND REOPERATION FOR MITRAL STENOSIS. *Dwight E. Harken, M.D., F.A.C.C., Harrison Black, M.D., Warren J. Taylor, M.D.* and *Laurence B. Ellis, M.D.* Harvard Medical School, Boston, Mass.

Deterioration after valvuloplasty has been analyzed in previous communications, but no detailed follow-up has as yet been available to correlate the reasons for initial failure with the quality of results obatined by the various types of reoperation.

The technics of reintervention include right- and left-sided simple direct transauricular pursestring entry, operating tunnel and open operations. Experience in over 150 cases is reviewed. More than half of these patients were originally operated on by us. The others were operated on elsewhere.

Reasons for recurrence, indications for reintervention, the type of reintervention and the results of this surgery constitute the basis of this presentation.

THE EFFECT OF CARDIAC ARRHYTHMIAS ON THE CIRCULATION OF THE VITAL ORGANS. *David Irving, M.D., Herbert Gold, M.D., F.A.C.C.* and *Eliot Corday, M.D., F.A.C.C.* Cedars of Lebanon Hospital, Los Angeles, Calif.

The blood flow of the cerebral, coronary, hepatic, renal and gastrointestinal organs was measured with the electromagnetic flowmeter during naturally occurring and artificially produced cardiac arrhythmias. It was demonstrated that the rapid cardiac arrhythmias which caused a drop in systemic blood pressure caused a marked reduction in all the vital organs. However, the vasomotor reaction of each vital organ was different.

THE CHOLESTEROL LOWERING EFFECT OF THYROID ANALOGUES IN THYROID SENSITIVE PATIENTS WITH HEART DISEASE. *Henry L. Jaffe, M.D., Eliot Corday, M.D., F.A.C.C.* and *Herbert Gold, M.D., F.A.C.C.* University of Southern California and University of California, Los Angeles, Calif.

Patients with hypercholesterolemia have been treated with a thyroid analogue (tetraiodothyfromic acid). It was demonstrated that the blood cholesterol could be lowered significantly. The patients selected for this study were mainly those with severe coronary artery disease who had been previously made hypometabolic with radioactive iodine. The patients had been free of anginal pain for a period of at least two years following radioiodine therapy. The blood cholesterol level of all these patients was markedly elevated. Most of the patients were sensitive to thyroid and previously could not tolerate doses larger than $^1/_{10}$ to $^1/_4$ grain of thyroid per day because it would induce anginal attacks.

Placebo medication was first administered to this group of patients, and the control blood cholesterol and electrolyte studies were determined at regular intervals of two weeks. The thyroid analogues were then given to these patients and subsequent serial blood studies demonstrated that the blood cholesterol level could be lowered as much as 280 mg. per cent. The average reduction was 112 mg. per cent over a six-week period. As a rule, the metabolism was not elevated by the thyroid analogue. Most of the patients could tolerate the thyroid analogue in sufficient dosage to significantly reduce blood cholesterol.

Tetraiodothyfromic acid is an effective anticholesterol agent which appears to be safe to use in patients with severe heart disease.

AUTOREGULATION OF INTESTINAL BLOOD FLOW. *Paul C. Johnson, M.D., with the technical assistance of Stuart L. Graham.* Indiana University School of Medicine, Indianapolis, Ind.

Previous experiments have shown that the arterial vessels of the intestine are responsive to changes in portal venous pressure, with pressure elevation causing arterial constriction. The purpose of this study was to determine whether these vessels respond in a similar fashion to changes in arterial pressure.

In thirty-nine pressure-flow studies on segments of terminal ileum, resistance to flow decreased with pressure reduction in 72 per cent of the experiments and increased in 28 per cent. The passive increase in resistance with pressure reduction was seen primarily shortly after the surgical procedure was completed. Thus, it appears that the arterial vessels of the intestine are not ordinarily passively distensible with changes in arterial pressure. As a result of this vascular reaction, the influence of arterial pressure on blood flow is at least partially counteracted. The mechanism of this autoregulation of flow is not a local reflex, a change in interstitial fluid volume or a change in tone of the intestinal muscle. Changes in concentration of aerobic or anaerobic metabolites and oxygen tension of the tissues were likewise eliminated. It is concluded that autoregulation of intestinal blood flow is a result of the sensitivity of vascular smooth muscle to change in arterial pressure (a myogenic response).

SURVEY OF THE PROBLEM OF PATENT DUCTUS ARTERIOSUS. *George Kaiser, M.D.* Indiana University Medical Center, Indianapolis, Ind.

Over a ten-year period, no deaths followed ductal division in typical patients with no known pulmonary hypertension. The records of over fifty patients with known hypertension of varying degrees are reviewed. Success has been achieved in several with obvious reversal. Three deaths occurred: one during postoperative bronchoscopy for atelectasis, two in patients believed to represent cases with retention of high fetal resistance (one at operation, one of unexplained cause on fourth postoperative day). No deaths occurred in twenty-two cases of coarctation and patent ductus. Also reviewed are cases complicated by intracardiac shunt with and without coarctation.

RESULTS OF COMBINED TRANSTHORACIC LEFT AND PERCUTANEOUS RIGHT HEART CATHETERIZATION IN VALVULAR LESIONS OF THE LEFT HEART. *Paul Kezdi, M.D., F.A.C.C.* Chicago Wesley and Passavant Memorial Hospitals, and the Northwestern University Medical School, Chicago, Ill.

Combined left and right heart catheterizations were performed in 150 patients with lesions of the left side of the heart by the transthoracic approach and simultaneous percutaneous catheterization of the right heart. The latter required no fluoroscopy. Cardiac output and pressure gradients were determined simultaneously and valvular areas were calculated. The largest single group studied had pure mitral stenosis. The rest had mitral stenosis and regurgitation, aortic stenosis, combined aortic and mitral lesion and non-valvular heart condition in decreasing order. Valuable information was obtained supplementing the clinical findings and aiding the clinician in his decision in recommending surgical treatment. In a significant number of instances, the findings were contrary to the clinical impression. In combined valvular lesions, the predominant lesion could be evaluated with great accuracy.

Characteristic hemodynamic changes of the different valvular lesions obtained by left heart catheterization are discussed. Hemodynamic results of aortic valvotomy are presented in patients studied by left heart catheterization pre- and postoperatively.

Complications were relatively few and minor. There were no deaths and cardiac tamponade did not occur.

EXPERIMENTAL STUDIES WITH MITRAL VALVE REPLACEMENT. *Harold King, M.D.* Indiana University Medical Center, Indianapolis, Ind.

To date, results of total replacement of a mitral valve leaflet with a plastic prosthesis have been dis ppointing. In contrast, results obtained with partial replacement of a mitral valve leaflet are encouraging.

HEMODYNAMIC EFFECTS OF BALLOON OBSTRUCTION OF THE ABDOMINAL AORTA AND CLOSED-CHEST EXTRACORPOREAL CIRCULATION IN EXPERIMENTAL MYOCARDIAL INFARCTION WITH SHOCK. *Leslie A. Kuhn, M.D., F.A.C.C., Frank Gruber, M.D., Albert Frankel, M.D.* and *Sherman Kupfer, M.D.* The Mount Sinai Hospital, New York, N. Y.

The ability of extracorporeal circulatory support to produce a sustained increase in coronary perfusion pressure, and its effects on left ventricular work, cardiac output and systemic vascular resistance were investigated in closed-chest dogs with shock following plastic sphere coronary embolization.

In normal animals and in those with hypotension due to myocardial infarction, pumping of large volumes of blood (40 to 60 cc./kg./minute) from the venae cavae into the abdominal aorta failed to produce a rise in central aortic pressure. To raise central aortic pressure in these animals it was necessary to increase vascular resistance. This was accomplished by inflating a balloon catheter inserted via a femoral artery into the abdominal aorta. Blood pumped from the superior vena cava supplied the distal aorta below the site of obstruction. In this manner, the circulation was "compartmentalized," leading to a rise in proximal aortic pressure with increased perfusion of the heart and the brain, and some diminution in distal aortic pressure. With this method, normal animals and those with myocardial infarction with shock demonstrated a sustained increase in central aortic (coronary perfusion) pressure and coronary flow, average central aortic mean pressure in twelve animals with shock rising from 73 to 139 mm. Hg. Left ventricular end diastolic and right atrial pressures remained normal. Left ventricular work diminished or remained unchanged despite the rise in central aortic pressure, due to shunting of a portion of the venous return into the distal aorta.

It is concluded that conventional technics of extracorporeal circulation, employing shunting from the veins to the abdominal aorta, are ineffective in raising coronary perfusion pressure unless there is severe congestive heart failure. To raise aortic pressure by mechanical means in experimental myocardial infarction with shock, it is necessary to increase vascular resistance.

PRACTICAL CLINICAL CORONARY ANGIOGRAPHY. *David Littmann, M.D., F.A.C.C., Frank Crowley, M.D.* and *David Dean, M.D.* V. A. Hospital, West Roxbury, Mass.

Visualization of the coronary arteries in the live subject can now be performed quickly, safely and with a minimum of discomfort. A specially formed polyethylene catheter is inserted into the root of the aorta by means of a modification of the Seldinger technic. It is percutaneously introduced through an area of local anesthesia over the right femoral artery. Radiopaque contrast substance is precisely injected into the coronary sinuses and rapid serial radiographs are obtained. Cardiac slowing is effected by bilateral carotid artery compression.

Fifty-five subjects have been studied by this method during the past year. With few exceptions, they were men with suspected coronary or rheumatic heart disease. A few had congenital anomalies. A majority of the coronary angiograms made by this method were of diagnostic quality and only ten were considered inadequate. The unidentified angiograms were separately read and compared with the clinical pattern as determined by conventional means. Excellent correlation was obtained. With one or two exceptions coronary vascular abnormalities were apparent in all patients with arteriosclerotic heart disease while none was detected in the few normal subjects and in patients with valvular or congenital disease. The vascular bed was understandably prominent and, at times, tortuous in the presence of ventricular hypertrophy.

Intrinsic coronary abnormalities included non-filling of a vessel on repeated injections despite good opacification of the corresponding sinus. However, this did not occur in the absence of unusual tortuosity and ramification of the remaining vessels. In some instances extraordinary multiplication and branching was noted and interpreted as evidence of collateral development. Occasionally, a veritable cascade of fine vessels was seen emanating from (or going to) an area of large vessel obstruction. Localized blocks were seen and an occasional instance of small aneurysmal dilatations. Moth-eaten areas of incomplete occlusion were also noted.

There were no important reactions to the procedure and no deaths. As a result of these studies several patients were operated upon for relief of the symptoms of coronary inadequacy. In each instance the radiographic findings were confirmed. Direct blood vessel surgery was not attempted when the angiograms revealed diffuse disease.

RELATIVE MITRAL INSUFFICIENCY AS A FACTOR IN PAROXYSMAL PULMONARY EDEMA. *Aldo A. Luisada, M.D., F.A.C.C., Aldo Jacono, M.D.* and *Marvin Kaplan, M.D.* The Chicago Medical School, Chicago, Ill.

The pressure curves from the pulmonary artery, left atrium and left ventricle (or aorta) were studied in seventeen dogs following stimulation of the central nervous system through intracisternal injection of veratrine. The systolic pressures of the aorta and left ventricle rose to extremely high levels. The diastolic pressures of the left ventricle rose in all experiments in which pulmonary edema developed. However, the level of the diastolic pressure was often not sufficiently raised to cause edema. A typical plateau pattern was observed in the left atrium of all dogs in which pulmonary edema developed. This systolic plateau, interpreted as the result of "relative" mitral insufficiency, further raised the mean pressure of the left atrium (and of the pulmonary vessels) above the threshold of transudation. It is postulated that this valvular insufficiency was caused by extreme dilatation of the left ventricle and represented an important factor in the mechanism of pulmonary edema.

CHLOROTHIAZIDE FOR ANGINA PECTORIS. A DOUBLE BLIND STUDY. *Monte Malach, M.D.* and *Benjamin A. Rosenberg, M.D.* Kings County Hospital Center, Brooklyn, N. Y.

A one-year study of the effect of therapy with chlorothiazide and a placebo on twenty-four patients with angina pectoris without apparent congestive heart failure was undertaken. Neither the patient nor the physician was aware of whether a placebo or chlorothiazide was being administered. At the end of six months patients who received placebo therapy were switched to chlorothiazide therapy and vice versa. The rationale for this therapy was to evaluate the effect of a diuretic agent for the abolition of latent congestive heart failure in patients with angina pectoris.

Of the twenty-four patients who were given chlorothiazide in doses of one 250 mg. tablet twice daily, fifteen (60 per cent) noted moderate to marked improvement of angina pectoris, with less daily or weekly sublingual nitroglycerine required; exercise tolerance was increased in thirteen (54 per cent); hypertension was reduced to normotension in nine (38 per cent); and a weight reduction was effected in nine (38 per cent). The electrocardiogram, ballistocardiogram and pulse rates were not notably affected. Leg cramps were noted in three, headaches and vertigo in two and a skin rash in one. No electrolyte abnormalities were detected by serum studies.

Of the twenty patients given a placebo, which was physically like the chlorothiazide, in doses of one tablet twice daily, a moderate to marked improvement was noted in six (30 per cent); exercise tolerance was increased in eight (40 per cent); hypertension was reduced to normotension in seven (35 per cent); and a weight reduction was effected in ten (50 per cent). The electrocardiogram, ballistocardiogram and pulse rates were not affected. Leg cramps, headaches, vertigo and bursitis of the left shoulder were noted in one each. Results of electrolyte studies on the serum remained normal.

The results indicate some slight improvement in angina pectoris with chlorothiazide when patients under identical conditions were given the drug or a like placebo. A similar study is now under way with hydrochlorothiazide.

A STUDY OF 17,000 ELECTROCARDIOGRAMS IN HEALTHY, FIT MALES. *G. W. Manning, M.D., F.A.C.C.* University of Western Ontario, Victoria Hospital, London, Ontario, Can.

The electrocardiograms of 17,000 healthy, fit, young (eighteen to twenty-four years of age) male candidates for Aircrew Training with the Royal Canadian Airforce have been studied. Abnormalities were found in 4 per cent of these subjects which, following further clinical and electrocardiographic studies, was reduced to less than 0.5 per cent considered as unfit for Aircrew Training.

In a number of instances the electrocardiogram brought to light organic cardiac lesions which had been overlooked or were not apparent in the initial medical examination. The place of the electrocardiogram in military selection has been studied in some detail during this work, and some conclusions with regard to its value are discussed.

In this study an opportunity has been afforded to review from a statistical standpoint a number of concepts reported in the literature with regard to the diagnosis of myocardial disease, such as the significance of T_1 less than T_3, the QRS amplitude criteria for left ventricular hypertrophy, the significance of deep inspiration on T_3 negativity, the incidence of RSR patterns in lead V_1, the height and duration of R in lead V_1, R-T depression following exercise and the like. A number of studies have been carried out to illustrate the upper limits of normal in the age group eighteen to twenty-four for these criteria.

SERUM GLUTAMIC OXALOACETIC TRANSAMINASE ACTIVITY IN ACUTE CORONARY THROMBOSIS WITH MYOCARDIAL INFARCTION. *Marsh McCall, M.D., F.A.C.C., Arthur Hertz, M.D., F.A.C.C.* and *Irving Rappaport, M.D.* Beekman-Downtown Hospital, New York, N. Y.

This is a two-year study of serum glutamic oxaloacetic transaminase activity in 253 consecutive patients admitted to the Medical Wards of the Beekman-Downtown Hospital, who had the provisional diagnosis of acute myocardial infarction on admission. Group 1 was composed of patients who had a history of acute onset of chest pain with electrocardiographic evidence of injury to the myocardium as shown by displacement of RS-T segments or abnormal QRS complexes with characteristic changes in the T waves. Group 2 consisted of patients with abnormal RS-T displacement with no evidence of abnormal Q waves and also patients with conduction defects without abnormal Q waves. Ten cubic centimeters of venous blood was withdrawn on admission, twelve hours later and daily for five days without reference to the fasting state. These specimens were refrigerated until transaminase activity was measured.

In 183 subjects in group 1, the SGOT activity was elevated above 44 units, which was our peak normal in sixty patients with compensated arteriosclerotic heart disease measured prior to the beginning of this study. There were thirty-eight deaths in this group. In five who died within six hours, the enzyme activity was normal. In three patients who recovered, the enzyme activity was also normal. All patients with classic electrocardiographic evidence of acute myocardial infarction who came to autopsy showed evidence of infarction at postmortem examination. Of sixty-two patients in group 2 the SGOT activity was elevated in sixteen and normal in forty-six. Scattergrams illustrate the marked differences in the distribution of the peak levels in these two groups.

BALLISTOCARDIOGRAPHIC EVALUATION OF THE CARDIOVASCULAR AGING PROCESS IN OVERTLY HEALTHY MALES AGED EIGHTEEN TO FIFTY-FOUR. *Arthur J. Moss, LT MC USNR*, U. S. Naval School of Aviation Medicine, Pensacola, Fla.

The cardiovascular aging process is universally present, but its early detection has been most difficult. The ballistocardiogram has been used for many years in the evaluation of cardiovascular function, and this technic offers a unique means of studying the change in cardiovascular dynamics with age. In the present study a healthy male population ranging in age from eighteen to fifty-four was studied on the Reeves ultra low-frequency acceleration ballistocardiograph.

The changing ballistocardiographic pattern with advancing age is elucidated. Criteria for ballistocardiographic abnormality are established in terms of accelerated cardiovascular aging, and the degree of abnormality is graded (1 to 3). The initial appearance of accelerated cardiovascular aging (grade 1 abnormality) is present in 25 per cent of the population by age thirty-five. A more severe degree of aging (grade 2) is evident in 30 per cent of the individuals by age fifty. There is an accelerated attack rate for the initial development of an abnormal ballistocardiogram in both the twenty-five to thirty-five and forty to fifty age ranges. The rate of conversion to a more severe grade ballistocardiographic abnormality increases significantly in the fifth decade.

The relationship between an abnormal ballistocardiogram, accelerated cardiovascular aging and coronary artery disease is discussed.

ORIGIN OF BOTH GREAT VESSELS FROM THE RIGHT VENTRICLE. *Henry N. Neufeld, M.D., F.A.C.C., James W. DuShane, M.D., Earl H. Wood, M.D., John W. Kirklin, M.D.* and *Jesse E. Edwards, M.D.* Mayo Clinic and Mayo Foundation Rochester, Minn.

Clinical, hemodynamic and pathologico-anatomic findings were studied in fifteen cases in which both great vessels arose from the right ventricle.

The cases were divided into two groups. In the first group the malformation was associated with large ventricular septal defects (eight cases). In the second group, in addition to a ventricular septal defect, obstruction to the outflow tract of the right ventricle was present. In both groups the aortic and pulmonic valves were found to be in approximately the same cross sectional body plane on pathologic examination. The condition under study may be difficult to distinguish from ventricular septal defect (when no pulmonary stenosis is present) and from the tetralogy of Fallot (when pulmonary stenosis exists). Such a distinction is important since the surgical methods of repair in origin of both great vessels from the right ventricle are different from those for either of the two common conditions with which it may be confused.

The clinical picture in the first group simulated that of a large ventricular septal defect associated with pulmonary hypertension. In seven of the eight cases the electrocardiogram showed prolonged P-R interval, mean QRS axis lying between -30 and -170 degrees and signs of right ventricular hypertrophy. This combination of electrocardiographic findings differs from the usual findings in large ventricular septal defects. The physiologic findings showed equalization of pressures in the systemic and pulmonary circulation. It is thought that demonstration by catheter positions that the aortic valve lies at the same cross sectional body level as the pulmonary valve in the anteroposterior view and anteriorly in the lateral view is a diagnostic indication that both great vessels may arise from the right ventricle. In some cases oxygen saturation of blood in the pulmonary artery approached or equaled that in the aorta, indicating that relatively complete

mixing of pulmonary venous and systemic venous blood had occurred in the outflow tract of the right ventricle in these individuals.

In the second group the clinical picture of tetralogy of Fallot was evident. These two malformations can be distinguished by demonstration of the anatomic relationship of the pulmonary and aortic valves to each other by catheter position during cardiac catheterization or selective angiocardiography or by both means.

HEMODYNAMIC EFFECTS OF INTRAVENOUSLY ADMINISTERED DEXTROSE AND UREA. *Mario Onnis, M.D.* Indiana University Medical Center, Indianapolis, Ind.

Many of the hemodynamic effects of intravenously administered dextrose and urea are similar: a transient initial fall in blood pressure, a transient abrupt increase in cardiac output and a diuresis. Dextrose, however, causes a marked increase in renal blood flow while urea causes no increase but rather a questionable slight fall. Renal oxygen consumption increases upon administration of urea.

QUANTITATIVE CRITERIA PERMITTING THE IDENTIFICATION AND EVALUATION OF HEMODYNAMICS BY MEANS OF THE ELECTROCARDIOGRAM. *Ramiro H. Pavon Caballero, M.D., F.A.C.C.* Holguin, Cuba.

Quantitation of ventricular overloads and ventricular hypofunctions from the electrocardiographic findings has provided a new quantitative method: ventricular estimate (VE %). This may help in evaluating the hemodynamics of the ventricles by means of the electrocardiogram.

Analytical studies concerning electrocardiographic-hemodynamic correlations were made in children with congenital heart diseases and in this paper we report only the results in pulmonary stenosis. A direct relationship between the intensity of right ventricular overload (RVE %) and the right ventricular systolic pressure was disclosed, so permitting integration of the formula:

$$RVSP = RVBP + (HE \times RVE\ \%)$$

instead of

$$y = a + bx$$

Thus an indirect estimation of right ventricular systolic pressure by means of the electrocardiogram is permitted. Therefore an evaluation of the degree of the pulmonary stenosis is possible since right ventricular systolic hypertension is the characteristic hemodynamic finding in this entity.

Such an indirect evaluation of RVSP in pulmonary stenosis represents an approach of the electrocardiographic method to the evaluation of results of corrective surgery, because the hemodynamic evolution after pulmonary valvulotomy can be followed without the need to subject the patients to repeated cardiac catheterization studies.

STUDIES OF CORONARY SINUS FLOW. *John Ponzer, M.D.* Indiana University Medical Center, Indianapolis, Ind.

A good method for measuring coronary sinus flow directly has been developed. Studies are presented to show effect of vasopressors, intravenously administered dextrose, hypothermia and hypovolemia.

THE VALUE OF PATCH GRAFTS IN SURGERY OF THE SUPERIOR VENA CAVA. *Angelo Riberi, M.D.* and *Daniel T. Pompey, M.D.* St. Elizabeth Hospital, Youngstown, Ohio.

Replacement of the superior and inferior vena cava has been very unsatisfactory. A number of reports have shown complete or partial failure of homologous and plastic materials. Our own work has indicated the unsuitability of autogenous pericardial tubes. Better results were obtained with heterologous (cow) aorta. Although we were eventually successful in bridging defects in the superior vena cava with autogenous aortic grafts and pedicle tubes created from the right atrium and appendage we always believed that sometimes a minor procedure could be of value in limited cases of involvement or of injury to only part of the venous wall, without true superior vena caval syndrome.

For this purpose the following experiment was carried out in dogs. Through a right third intercostal space thoracotomy, the superior vena cava was exposed, dissected free and excluded from the circulation by means of two clamps one applied, at the entry of the superior intercostal vein and the other just above the opening of the azygos vein. About 50 per cent of its flattened wall was then excised and replaced with a fine nylon patch. This was sutured in place with a continuous everting suture of No. 5-0 silk on an atraumatic needle. As a routine, one single dose of 50 mg. of heparin was given intravenously after closure of the chest.

All animals survived. These animals were studied three weeks and seven months postoperatively, either by cavogram or postmortem examination. No thrombosis, narrowing or perivenous fibrosis was observed. In all the animals the graft became rapidly covered with a thin layer of fibrin and then endothelized and, grossly, it was almost indiscernible from the normal contiguous venous wall. Patch graft of the superior vena cava with fine nylon was therefore completely uccessful under the conditions of this experiment.

EFFECT OF INFLATION OF PRESSURE SUIT OVER THE LOWER HALF OF THE BODY ON PULMONARY DIFFUSING CAPACITY FOR CARBON MONOXIDE AND THE PULMONARY CAPILLARY BLOOD VOLUME. *Joseph C. Ross, M.D., Thomas Lord, Glenn Ley* and *Gene Maddock.* Indiana University School of Medicine, and the V. A. Hospital, Indianapolis, Ind.

Theoretically, the pulmonary diffusing capacity (D_L) increases when pulmonary capillary blood volume (V_c) increases. Production of pulmonary vascular engorgement by the inflation of an aviator's G-suit over the lower half of the body has provided a convenient way to study the characteristics of the pulmonary capillary bed, particularly as to whether the pulmonary capillaries can be passively dilated or opened. Breath-holding D_L was determined in four seated and six supine subjects at rest and with inflation of the suit. To estimate the increase in pulmonary vascular pressures produced by the suit, the central venous pressure (CVP) was measured by a catheter in the superior vena cava. The four seated subjects had a mean control D_L of 37 ml./minute/mm. Hg with an increase to 42.7 ml./minute/mm. Hg when the CVP was increased 38 mm. Hg by inflation of the suit. Six supine subjects had a mean control D_L of 38.8 ml./minute/mm. Hg with an in-

crease to 43.6 ml./minute/mm. Hg when CVP was increased 13 mm. Hg. Using the method of Forster and co-workers, the pulmonary capillary blood volume (V_c) and the true diffusing capacity of the pulmonary membrane (D_m) were calculated from the values of D_L determined at different alveolar O_2 tensions in two of the seated subjects. In these two subjects, mean control D_L was 36.3 ml./minute/mm. Hg and increased to 52 ml./minute/mm. Hg with inflation of the suit. Mean D_m at rest was 68.2 ml./minute/mm. Hg with an increase to 79.5 ml./minute/mm. Hg during inflation of the suit. Mean V_c at rest was 112 ml. and mean V_c during suit inflation was 221 ml. These studies indicate that the pulmonary capillary bed can be passively enlarged by dilatation of patent capillaries and/or by opening of previously closed capillaries.

THE VECTORCARDIOGRAM IN DIRECT POSTERIOR WALL MYOCARDIAL INFARCTION. *Edwin L. Rothfeld, M.D., Fred W. Wachtel, M.D., William S. Karlen, M.D.* and *Arthur Bernstein, M.D., F.A.C.C.* Newark Beth Israel Hospital, Newark, N. J.

In posterior wall myocardial infarction, there is a loss of electrical forces directed to the left and posteriorly so that forces oriented to the right and anteriorly are enhanced. This results in prominent R waves in right precordial leads. Employing the cube reference system, vectorcardiograms were obtained in six cases of myocardial infarction in which tall R waves were displayed in right precordial leads. In all cases, the initial portion of the QRS sE-loop was displaced markedly to the right and anterior and showed a bizarre contour and delay in inscription.

The vectorcardiogram is of major diagnostic import in confirming the diagnosis of direct posterior myocardial infarction and in differentiating it from other causes of prominent R waves in right precordial leads, such as right ventricular hypertrophy and right bundle branch block which can be most confusing in cases in which there is no history of myocardial infarction.

EMOTIONAL STRESS AND CORONARY HEART DISEASE IN PHYSICIANS. *Henry I. Russek, M.D., F.A.C.C.* U. S. Public Health Service Hospital, Staten Island, N. Y.

In previous investigations, it was found that emotional stress of occupational origin was far more significant in the etiologic picture of coronary heart disease than a prodigiously high fat diet, heredity, obesity, physical exercise or the use of tobacco. In order to further test this finding, a survey was made by means of a questionnaire to determine the incidence of recognized clinical coronary heart disease among physicians in two medical specialties which are manifestly dissimilar with respect to daily occupational stresses. One thousand letters were sent to doctors certified by the American Board of Anesthesiology, and one thousand letters to doctors certified by the American Board of Dermatology. Since it is acknowledged that the duties of the dermatologist, in general, are considerably less stressful than those of the anesthesiologist, significant differences in the incidence of coronary heart disease were to be anticipated if emotional stress is a major etiologic factor in this disorder. The finding of a higher frequency of coronary artery disease in general practitioners as compared with medical specialists by Morris in England, would also lead to similar expectation.

The results, based on an analysis of more than one thousand replies to the questionnaire survey, revealed that coronary disease was significantly more prevalent in anesthesiologists than in dermatologists in all age groups from forty to sixty-nine years. Among anesthesiologists, the disease was two and a half times more prevalent in the forty to forty-nine year age group, three times more prevalent in the fifty to fifty-nine year age group and four times more prevalent in the sixty to sixty-nine year age group. Moreover, angina pectoris and myocardial infarction occurred an average of eight years earlier in anesthesiologists than in dermatologists. The results strongly confirm previous findings which have indicated that emotional stress of occupational origin is a potent factor in the pathogenesis of coronary heart disease in the American male.

EFFECT OF INTRAVENOUS FAT EMULSIONS ON HUMAN BLOOD VISCOSITY. *Martin A. Shearn, M.D.* and *Aristides Gousios, M.D.* Kaiser Foundation Hospital, Oakland, Calif.

The effect of intravenously administered fat emulsion on the viscosity of human blood was investigated because (1) hyperlipidemia in animals has been shown to result in increased blood viscosity (Swank) and (2) increased blood viscosity has been implicated in the pathogenesis of thrombosis.

Other investigators have employed viscometers with tube lumens smaller than that requisite for laminar flow. Since, in man, major thrombotic episodes occur in vessels of medium caliber (coronary or cerebral arteries, femoral vein, etc.), we determined blood viscosity by a simple, reproducible technic that utilized laminar flow, thus more accurately reflecting the situation in medium-sized vessels. The coefficient of variation as determined by a two-way analysis of variance on the first 103 determinations was 2.2 per cent.

In thirteen hospitalized subjects in the basal state, blood viscosity was determined in triplicate before and after injection of 600 ml. of an emulsion containing 90 gm. of lipids. All serums became extremely turbid. In some instances the total blood lipid content increased threefold after injection of the emulsion. Despite the magnitude of this rise, blood viscosity showed no significant change.

CARDIOVASCULAR FINDINGS IN CHILDREN WITH SICKLE CELL ANEMIA. *Herbert Shubin, M.D., Morse J. Shapiro, M.D., Ruebin Kaufman, M.D.* and *David C. Levinson, M.D., F.A.C.C.* Cedars of Lebanon Hospital, Los Angeles, Calif.

Seven children from six to sixteen years of age with hematocrits between 18 and 27 per cent and hemoglobin S in excess of 90 per cent showed the following cardiovascular features: (1) exertional dyspnea and fatigue; (2) fixed splitting of the second heart sound on deep inspiration; (3) third "filling" heart sound in five of the seven children; (4) systolic murmur of grade 2 intensity or louder, most prominent over the upper left sternal border; (5) roentgenographic evidence of diffuse cardiomegaly and increased pulmonary vascularity; (6) abnormal electrocardiograms in four; and (7) increased blood and plasma volumes.

Right heart catheterizations in these seven patients revealed the following: (1) normal vena caval, right atrial, right ventricular, pulmonary artery and wedged pulmonary artery pressures; (2) normal pulmonary

vascular resistances at rest and with exercise; (3) cardiac indices averaging twice normal; (4) increased stroke indices; (5) arterial oxygen unsaturation at rest and after breathing 100 per cent oxygen in all cases; (6) relatively small arteriovenous oxygen differences at rest and with exercise; (7) coronary sinus oxygen saturations below 40 per cent; (8) an abnormal Valsalva response. The significance of these findings is discussed.

HYPERURICEMIA AND HYPERGLYCEMIA IN ACUTE MYOCARDIAL INFARCTION. *Maxwell Spring, M.D., Mehmet Cavusoglu, M.D., Yung Ching Chu, M.D.* and *Christina Artymowska, M.D.* City Hospital, Elmhurst, N. Y.

Hyperuricemia and hyperglycemia can occur in acute myocardial infarction. The purpose of this study was to investigate the incidence of and relationship between the two and the implications to be derived therefrom.

Twenty-five patients with proved myocardial infarction were studied. Four patients died before their studies were completed. Autopsy confirmed the diagnosis of myocardial infarction in each. Twenty-one patients completed the entire program, seventeen males and four females. Ages ranged from thirty-six to eighty-five and fifty to seventy-two, respectively. None of the patients had a history of gout or showed any manifestation of gout. Only one was known to have diabetes, a woman aged sixty-nine.

Fasting blood sugar, uric acid, transaminase, C-reactive protein, erythrocyte sedimentation rate, cholesterol and white blood counts were performed at weekly intervals during hospitalization. A glucose tolerance test and the steroid modification using 20 to 25 mg. of prednisone were performed during the fourth week of illness preceded by a three-day preparation with a 300 gm. carbohydrate diet. A uric acid level of 6 mg. or above and a two-hour blood sugar level above 140 mg. per cent during the glucose tolerance test were considered abnormal.

Sixteen patients (76 per cent), thirteen males and three females, exhibited hyperuricemia. Three of the four patients who died also exhibited hyperuricemia. The uric acid level ranged from 6 to 11 mg. per cent. In the patients who survived, the uric acid level usually remained elevated during the entire hospital stay. In a follow up on one patient the uric acid level returned to normal after seven weeks.

Twelve patients (57.1 per cent), ten males and two females, had an abnormal glucose tolerance curve. In five of these, it became positive after the steroid modification of this test was used.

Nine patients (42.8 per cent), eight males and one female, had both an elevated uric acid level and an abnormal glucose tolerance curve.

There did not seem to be any correlation between the height of the serum transaminase and the level of the uric acid nor was there any between the location and extent of the infarct and the uric acid level.

CHOLESTEROL CRIPPLES. *G. Douglas Talbott, M.D.* Dayton, Ohio.

There is increasing evidence that hyperlipidemia may be related to coronary atherosclerosis. There has been a tendency to relate cholesterol determinations in the blood to the presence or the absence of this disease. Recent serious doubts concerning this relationship have been raised by many investigators. Triglyceride metabolism may have a closer relationship to coronary atherogenesis than cholesterol metabolism. The purpose of this study, however, is not an attempt to settle this dispute, but to statistically demonstrate that cholesterol levels are by themselves not a reflection of the rest of the lipid elements in the blood stream.

Prisoners at the county prison were placed in solitary confinement for two weeks and placed on a prefrozen, precooked, analyzed diet; these prisoners were then given cottonseed oil intravenously. Fasting blood samples were obtained and subsequent samples gathered immediately after the infusion of oil, at two hours, four hours and twenty-four hours. Complete lipid analyses were performed on each of these blood samples. This lipid analysis included blood cholesterol, cholesterol esters, phospholipids, phospholipid esters, total esterified fatty acids, neutral fatty acids, total lipids and alpha- and beta-lipoproteins. Athero index and total turbidity units were also calculated.

The results were then subjected to a statistical analysis to determine if cholesterol had any valid statistical relationship to the rest of these blood factors. It was statistically shown that cholesterol cannot be used to predict or ascertain other blood elements, such as triglycerides or total lipids. Additional lipid analysis was then performed on patients with known coronary artery disease; these blood analyses were again subjected to statistical evaluation.

It does not appear justified on the strength of these data to perform cholesterol determinations and draw conclusions concerning the rest of the lipid elements in the blood. Since there is serious doubt that cholesterol bears a closer relationship to atherogenesis than the other blood lipid analyses there is also serious doubt that clinical conclusions may be drawn from single blood cholesterol determinations. However, because of the simplicity and widespread practice of making single blood cholesterol determinations and drawing clinical conclusions there is an increasing tendency to produce "cholesterol cripples." The problem of cholesterol cripples is becoming increasingly important as the lay literature contains greater quantities of material about dietary fats and blood cholesterol.

THE FEASIBILITY OF ANTICOAGULANT THERAPY IN CORONARY ARTERY DISEASE WITH CONGESTIVE HEART FAILURE. A CLINICAL STUDY USING PHENYLINDANDIONE. *Ralph M. Tandowsky, M.D., F.A.C.C.* and *Walter A. Flieg, M.D.* Hollywood, Calif.

The frequency of thromboembolic phenomena complicating congestive heart failure is a common clinical entity. Because of the underlying physiopathologic change in this syndrome, inefficient function of both arterial and venous systems predispose to inefficient flow with subsequent laking of blood and change in blood viscosity. This change is especially prevalent in the presence of previously diseased blood vessels. With the extreme fatigue observed in congestive heart failure the accompanying physical inactivity adds to the severity of blood stagnation. It has been demonstrated that the liver, when heavily congested, attempts to combat this thromboembolic tendency but this type of compensation is inadequate. Many drugs used in the treatment of congestive failure are known to lessen the prothrombin time and favor thromboembolism. Among those used most commonly are digitalis, the purin bodies and mercurials.

Clinical observations made on a group of patients with known coronary disease and congestive failure revealed incomplete digitalization and little relief of symptoms prior to the institution of anticoagulant therapy. Those receiving sufficient anticoagulants and then digitalized, reacted in a satisfactory manner both subjectively and objectively. This effect was also noticeable when mercurial diuretics were used. Based on these observations this preliminary study was undertaken with a group of these patients with and without anticoagulant therapy. Prothrombin time and other laboratory procedures were carried out on the entire group. Phenylindandione proved to be a convenient and satisfactory anticoagulant for this study. No untoward complications resulted from its use. Those receiving anticoagulants responded to digitalis and diuretics in a more satisfactory manner and thromboembolic complications were fewer. The results obtained from this preliminary study suggest the value of anticoagulant therapy in congestive heart failure, particularly when it complicates coronary artery disease.

HEPATIC BLOOD FLOW STUDIES. *Shigeru Teramoto, M.D.* and *Harris B. Shumacker, M.D.* Indiana University Medical Center, Indianapolis, Ind.

This represents an experimental study of total hepatic flow by a direct method. It includes studies in normovolemic and hypovolemic dogs. Hypovolemia induces a marked decrease. In hypovolemic and normovolemic dogs, the intravenous administration of glucose, saline and blood increase hepatic flow as do vasopressors.

PARTIAL CARDIOPULMONARY BYPASS WITH THE PUMP-OXYGENATOR AS A SUPPORTIVE MEASURE: PRELIMINARY LABORATORY STUDIES. *John V. Thompson, M.D., F.A.C.C., Ray J. Gratz, M.D.* and *A. Wayne Schmalhausen, M.D.* Indiana University School of Medicine, Indianapolis, Ind.

It seems desirable to develop a mechanical means of supporting the interrelated circulatory and respiratory functions in many conditions until a physiologic adjustment can take place.

A bubble oxygenator was utilized in these experiments. Sodium pentothal was administered intravenously for anesthesia. Four heparinized animals were perfused originally for short periods of one and a half to three hours with a femoral-femoral bypass, but without intubation. It was found that a gravitational venous return permitted an average perfusion rate of 25 cc./kg. or approximately 25 per cent of the estimated cardiac output. All animals survived.

An additional four animals were then subjected to severe abnormal physiologic states during acute experiments. These dogs were intubated and a unilateral thoracotomy was performed on them with isolation of the main bronchus and preservation of the pulmonary vessels. Blood oxygen saturation and pressure recordings were obtained from the left femoral and brachial arteries. A marked decrease in arterial oxygen saturation developed after clamping of the bronchus as blood circulated through an unventilated lung. Partial bypass perfusion resulted in a marked increase in arterial saturation when the bronchus was clamped. This occurred only in the femoral artery during femoral to femoral perfusion, but appeared in the left brachial artery during femoral vein to right carotid artery bypass. In addition, reduction of the ventricular output produced by circumferential restricting tapes caused a marked fall in blood pressure which was corrected by the perfusion.

Femoral vein to carotid artery perfusions were later carried out in a group of eight normal heparinized animals over periods averaging seven hours with no positive pressure ventilation. The heparin dosage was adjusted by the coagulation time. Observations were made during the procedure, at the end of the perfusion and during the postoperative period on the blood coagulation, acid-base, electrolyte and protein factors. A reduction in platelets, bicarbonate and albumin with early return to normal was noted. An accumulation of air bubbles in the apparatus caused the death of some animals and was apparently corrected by a reduction in the oxygen flow rate. Distal perfusion of the cannulated artery and drainage of the distal vein appeared to be beneficial.

LEFT ATRIAL PUNCTURE AND THE DIAGNOSIS OF MITRAL REGURGITATION. *Mendel Wassermil, M.D., Donald L. Warkentin, M.D.* and *Abe Ravin, M.D.* General Rose Memorial Hospital, Denver, Colo.

Left heart catheterization was developed during the early 1950's to be used as an additional tool for the precise diagnosis of left-sided valvular lesions. The presence of aortic valvular involvement or of "silent" mitral stenosis may readily be discovered in this manner. When mitral stenosis and regurgitation occur in combination it is of prime importance to ascertain the predominant lesion so that proper surgical technics may be utilized. Various investigators have set forth criteria for the diagnosis of mitral regurgitation from an analysis of the left atrial pressure contour. Several formulas have been devised which purport to single out the predominance of mitral regurgitation.

We have recently completed a series of fifty left atrial punctures. Twenty-six of these patients underwent surgery with a preoperative diagnosis of predominant mitral stenosis. Thirteen of these patients had either 2 plus or 3 plus regurgitation at surgery. By using various criteria derived from left atrial pressure contours a correlation with the operative findings was attempted. No consistent correlation between mitral regurgitation and any criterion, singly or in combination, was found.

Although complications are few following left atrial puncture the morbidity is quite significant. In our series the reliability of this procedure in diagnosing mitral regurgitation proved quite disappointing. It is our opinion that with present means of analysis left atrial puncture affords little advantage over clinical judgement or right heart catheterization in the diagnosis of mitral regurgitation.

PAIN IN THE CHEST ASSOCIATED WITH HYPERTENSION OF THE LESSER CIRCULATION. *William H. Wehrmacher, M.D., F.A.C.C.* Northwestern University Medical School, Chicago, Ill.

Pain in the chest frequently perplexes the physician when its cause is not apparent, and almost invariably arouses fear in the patient. An important type of such pain is associated with hypertension of the lesser circulation, but it is frequently confused with other types of pain in the chest, particularly that arising from coronary artery disease. It requires different treatment and has a different prognosis. Heretofore called "angina hypercyanotica" or "pulmonary hypertensive pain," it is not

adequately designated by either term in the light of newer observations.

Clinical features, such as the duration of pain, variations induced by respiration, response to drugs or oxygen, signs of pulmonary disturbance or certain specific cardiovascular alterations and the presence of concurrent pulmonary disease, may be sufficient to distinguish the syndrome from others which may simulate it. Of the several causes of pulmonary hypertension, we have studied 189 cases of mitral stenosis (in collaboration with Blonsky and Kezdi) and a series of cases of interatrial septal defect and of pulmonary stenosis (in collaboration with Kuroda and Kezdi). In these cases, functional alterations measured by cardiac catheterization are correlated with clinical, electrocardiographic and roentgenologic findings to assay the role of hypertension when it encompasses all or only a part of the lesser circulation. From these data, conflicting past observations and hypotheses regarding this syndrome appear in new perspective.

Rational treatment of the syndrome depends upon precise diagnosis and comprehension of the functional alterations which occur. Clinical anticipation permits propitious prophylactic management in some cases, but many cases are not recognized until the hypertension is already advanced. Some etiological factors can be controlled directly. Certain drugs and other measures dilate pulmonary vasculature to reduce pressure. Rest exceeds its extolled virtues in other manner of disease. The regimen for cardiac decomposition differs on y slightly from that appropriate under other circumstances. Symptomatic remedies such as oxygen, analgesia and sedation, may impair cardiopulmonary dynamics sufficiently to overshadow their concurrent beneficial actions and thus must be employed with circumspect judgement in this syndrome.

CARDIAC OUTPUT: OBSERVATIONS ON THE VALIDITY OF THE PRECORDIALLY MONITORED RADIOACTIVE DILUTION CURVE. *Sylvan L. Weinberg, M.D., F.A.C.C., G. Richard Grove, Ph.D., W. Warren Blanchard, B.S.* and *Robert E. Zipf, M.D.* Miami Valley Hospital, Dayton, Ohio.

The technic of determining cardiac output by obtaining a dilution curve from precordial monitoring of intravenously injected radioactive material has been widely used for several years. As in all dilution technics, regardless of the indicator substance used, the validity of the results depends on the accurate extrapolation of the descending limb of the dilution curve to the zero level. As pointed out by Hamilton many years ago, this extrapolation is necessary in any system in which recirculation occurs before the single passage past the monitoring point is completed.

In the precordial monitoring, the problem arises as to selection of the position of the scintillation probe. It has been apparent that the contour of the dilution curve may vary depending on the structures which underly the scintillation probe. For example, the contour of the dilution curve monitored from the right ventricle has a different appearance from that over the left ventricle or from a probe placed as to derive components from both ventricles.

We have approached this problem by using two scintillation probes with separate count rate meters and direct reading recorders giving two simultaneous dilution curves on the same strip chart. This method has enabled us to define the so-called right ventricular, left ventricular and combined dilution curves, and to document what, if any, differences in the cardiac output calculation occur as the result of probe positioning.

The results tend to support our previous conclusion that arbitrary positioning of the scintillation probe according to bony landmarks is a satisfactory technic. The results suggest that the cardiac output determination is essentially the same whether a so-called right ventricular, left ventricular or combined ventricular dilution curve is obtained. These findings emphasize the simplicity of the method and are encouraging for its wider application as a clinically useful method of studying cardiac output.

USE OF A NEW AMINE OXIDASE INHIBITOR IN THE TREATMENT OF ANGINA PECTORIS. *Sydney J. Weisman, M.D.* and *Samuel A. Weisman, M.D., F.A.C.C.* University of Southern California, Los Angeles, Calif.

The preparation used in this study is Ro 4-1634 (tersavid) an analog of iproniazid. The chemical formula is 1-benzyl, 2-trimethylacetylhydrazine.

Twenty patients, ten males and ten females, were followed up for periods up to ten months. Age distribution ranged from thirty-five to eighty years. All subjects had angina pectoris; nineteen had classic angina of effort, one angina decubitus. Exceptionally good results in the decrease of anginal pain occurred in fifteen patients, fairly good results in three and poor results in two. There was one death probably due to a massive myocardial infarction. The death could not be attributed to the drug.

Results of therapy with Ro 4-1634 were evaluated on the basis of change in consumption of nitroglycerine, and of change in ability to exert without pain. Since the mode of action is not completely understood, it was not considered wise to attempt to prevent all angina by increased dosage of the drug. It is possible that a false sense of security could result in the patient exerting to the point of danger without the forewarning of anginal pain. If therapy with relatively small dosage failed, no attempt was made to determine the patient's tolerance for the drug.

Untoward reactions have been rare and have consisted only of an orthostatic drop in blood pressure, noted in two cases. This was eliminated by decreasing the dosage. No electrocardiographic changes were observed.

MONAMINE OXIDASE INHIBITORS IN THE TREATMENT OF ANGINA PECTORIS: SELECTION OF PATIENT AND DRUG. *Joseph B. Wolffe, M.D., F.A.C.C.* Valley Forge Heart Hospital and Medical Center, Fairview Village, Pa.

The use of iproniazid for the symptomatic relief of angina pectoris has been open to question because of occasional hepatotoxic side effects.

The development of important analogues added to the therapeutic armamentarium for the symptomatic relief of angina pectoris. Three monamine oxidase inhibitors—niamid, tersavid and Marplan®—have been investigated by us.

Our report is based on a study of 200 patients to whom these drugs were administered at various times. The results were most encouraging. Care in selecting the proper monamine oxidase inhibitor in a given patient improves the result. Attention is called to occasional untoward effects.

College News

AMERICAN COLLEGE OF CARDIOLOGY

Ninth Annual Meeting

May 25–28, 1960, Claypool Hotel, Indianapolis, Indiana

Scientific Program

First Scientific Session

Indianapolis Section

Wednesday, May 25, 2:00–5:30 p.m.

Chairman: JOHN B. HICKAM, M.D.

SECTION I

1. A Comparison of Pulmonary Hemodynamics when Determined at Timed Intervals During Exercise in Patients with Pulmonary Emphysema and Hypertension.
   ROY H. BEHNKE, M.D., DOUGLAS H. WHITE, M.D. and JOHN F. WILLIAMS, JR., M.D.
2. Effect of Inflation of Pressure Suit over the Lower Half of the Body on Pulmonary Diffusing Capacity for Carbon Monoxide and the Pulmonary Capillary Blood Volume.
   GLENN LEY, M.D., THOMAS LORD, GENE MADDOCK and JOSEPH C. ROSS, M.D.
3. The Immediate Effect of Mitral Commissurotomy on Pulmonary Compliance.
   STUART BONDURANT, M.D., ROBERT KING, M.D. and HARRIS B. SHUMACKER, JR., M.D.
4. Autoregulation of Intestinal Blood Flow.
   PAUL C. JOHNSON, M.D.
5. Effect of Potassium and Digitalis on Ventricular Arrhythmias and A-V Conduction; a Reappraisal of Digitalis and Potassium Relationship.
   CHARLES FISCH, M.D., B. L. MARTZ, M.D. and FRED H. PRIEBE, M.D.
6. An Investigation of the Vasodepressor Response to Ganglionic Stimulating Doses of Acetylcholine.
   R. W. GARDIER, M.D., P. C. JOHNSON, M.D., R. P. ROESCH, M.D. and V. K. STOELTING, M.D.

3:30–4:00 p.m.—Intermission

Chairman: A. DUDLEY DENNISON, JR., M.D.

SECTION II

7. Survey of the Problem of Patent Ductus Arteriosus.
   GEORGE KAISER, M.D.
8. Observations on Embolism.
   ISIDOR MANDELBAUM, M.D.
9. Renal Autoregulation.
   GUSTAVO BOUNOUS, M.D., MARIO ONNIS, M.D. and HARRIS B. SHUMACKER, JR., M.D.
10. Estimation of State of Peripheral Arterial Tree from Electronic Pulse Wave Studies.
    JOE ARMBRUSTER, M.D.
11. Studies of Coronary Sinus Flow.
    JOHN PONZER, M.D.
12. Hepatic Blood Flow Studies.
    HARRIS B. SHUMACKER, JR., M.D. and ROBERT KING, M.D.

Fireside Conferences

Wednesday, May 25, 8:30–10:30 p.m.

1. Surgery of Acquired Heart Disease.
   CHARLES P. BAILEY, M.D., New York, N. Y. and DONALD B. EFFLER, M.D., Cleveland, Ohio.
2. Cardiovascular Response to Environment and Activity.
   GEORGE E. BURCH, M.D., New Orleans, La., HERMAN K. HELLERSTEIN, M.D., Cleveland, Ohio and LEON J. WARSHAW, M.D., New York, N. Y.

3. Traumatic Heart Disease.
   THOMAS W. MATTINGLY, M.D., Washington, D. C. and EMIL A. NACLERIO, M.D., New York, N. Y.
4. Life Stress and Heart Disease.
   LAURENCE E. HINKLE, JR., M.D., New York, N. Y. and ADRIAN M. OSTFELD, M.D., Chicago, Ill.
5. Available Methods for Management of Hyperlipemia.
   IRVINE H. PAGE, M.D., Cleveland, Ohio, JEREMIAH STAMLER, M.D., Chicago, Ill. and JOHN M. EVANS, M.D., Washington, D. C.
6. Indications for and Administration of Anticoagulants in Cardiovascular Disease.
   IRVING BROTMAN, M.D., Washington, D. C., WILLIAM T. FOLEY, M.D., New York, N. Y. and E. STERLING NICHOLS, M.D., Miami, Fla.
7. Office Use of Phonocardiography.
   E. E. EDDLEMAN, JR., M.D., Birmingham, Ala. and ALDO A. LUISADA, M.D., Chicago, Ill.
8. Unrecognized Myocardial Infarction.
   SIMON DACK, M.D., New York, N. Y. and MYRON PRINZMETAL, M.D., Los Angeles, Calif.
9. Management of Arrhythmias.
   E. GREY DIMOND, M.D., Kansas City, Kan. and BERNARD LOWN, M.D., Boston, Mass.
10. Connective Tissue Disorders (Collagen) in Cardiovascular Diseases.
    SIDNEY ROTHBARD, M.D., New York, N. Y. and JOHN H. TALBOTT, M.D., Chicago, Ill.
11. Chronic Bronchitis, Emphysema and Heart Disease.
    ROSS C. KORY, M.D., Wood, Wis., GEORGE R. MENEELY, M.D., Nashville, Tenn. and JOHN B. HICKAM, M.D., Indianapolis, Ind.
12. Life Expectancy of the Patient with Heart Disease.
    GEORGE W. CALVER, M.D., Washington, D. C., GEORGE R. HERRMANN, M.D., Galveston, Texas and HARRY E. UNGERLEIDER, M.D., New York, N. Y.
13. Physiology and Treatment of Disorders of the Coronary Circulation.
    ELIOT CORDAY, M.D., Los Angeles, Calif. and RICHARD GORLIN, M.D., Boston, Mass.
14. Treatment of Angina Pectoris.
    ARTHUR M. MASTER, M.D., New York, N. Y., HENRY I. RUSSEK, M.D., Staten Island, N. Y. and JOSEPH B. WOLFFE, M.D., Fairview Village, Pa.

Second Scientific Session

Thursday, May 26, 9:00–12:30 a.m.

Chairman: LOUIS F. BISHOP, M.D.

1. Diagnosis and Treatment of Cardiac Tumors.
   CRAWFORD W. ADAMS, M.D., HAROLD A. COLLINS, M.D. and JOSEPH H. ALLEN, M.D., Nashville, Tenn.
2. Serum Glutamic Oxaloacetic Transaminase Activity in Acute Coronary Thrombosis with Myocardial Infarction.
   MARSH MCCALL, M.D., ARTHUR HERTZ, M.D. and IRVING RAPPAPORT, M.D., New York, N. Y.
3. Results of Combined Transthoracic Left and Percutaneous Right Heart Catheterization in Valvular Lesions of the Left Heart.
   PAUL KEZDI, M.D., Chicago, Ill.
4. Restenosis and Reoperation for Mitral Stenosis.
   DWIGHT E. HARKEN, M.D., HARRISON BLACK, M.D., WARREN J. TAYLOR, M.D. and LAURENCE B. ELLIS, M.D., Boston, Mass.
5. Practical Clinical Coronary Angiography.
   DAVID LITTMANN, M.D., FRANK CROWLEY, M.D. and DAVID DEAN, M.D., West Roxbury, Mass.
6. To be read if time permits: The Current Status of Bile Acid Metabolism with Particular Reference to Cholesterol.
   ROBERT B. FAILEY, JR., M.D., Indianapolis, Ind.

10:30–11:00 a.m.—Intermission

Chairman: GEORGE R. MENEELY, M.D.

7. Hemodynamic Effects of Balloon Obstruction of the Abdominal Aorta and Closed-Chest Extra-Corporeal Circulation in Experimental Myocardial Infarction with Shock.
   LESLIE A. KUHN, M.D., FRANK GRUBER, M.D., ALBERT FRANKEL, M.D. and SHERMAN KUPFER, M.D., New York, N. Y.
8. The Normal QRS Vectorcardiogram in Infants and Children from Birth to Fifteen Years.
   HOMOBONO B. CALLEJA, M.D., RAYMOND

E. Barker, M.D. and Ray W. Kissane, M.D., Columbus, Ohio.

9. A Study of 17,000 Electrocardiograms in Healthy Fit Males.
   G. W. Manning, M.D., London, Ontario, Can.
10. The Vectorcardiogram in Direct Posterior Wall Infarction.
    Edwin L. Rothfeld, M.D., Fred W. Wachtel, M.D., William S. Karlen, M.D. and Arthur Bernstein, M.D., Newark, N. J.
11. Ballistocardiographic Evaluation of the Cardiovascular Aging Process in Overtly Healthy Males Ages 18–54.
    Lt. Arthur J. Moss, MC, USNR, Pensacola, Fla.
12. Experience in Cinefluorography.
    Robert S. Green, M.D., Cincinnati, Ohio.

Third Scientific Session

Thursday, May 26, 2:00–4:30 p.m.

CONVENTION GUEST LECTURE

Introduction: Osler A. Abbott, M.D., *President*

Some Prevalent Errors in the Practice of Cardiology.
Samuel A. Levine, M.D., Boston, Mass.

3:00–3:30 p.m.—Intermission

Chairman: E. Grey Dimond, M.D.

1. Origin of Both Great Vessels from the Right Ventricle.
   Henry N. Neufeld, M.D., James W. DuShane, M.D., Earl H. Wood, M.D., John W. Kirklin, M.D. and Jesse E. Edwards, M.D., Rochester, Minn.
2. Cardiovascular Findings in Children with Sickle Cell Anemia.
   Herbert Shubin, M.D., Morse J. Shapiro, M.D., Reubin Kaufman, M.D. and David C. Levinson, M.D., Los Angeles, Calif.
3. Pain in the Chest Associated with Hypertension of the Lesser Circulation.
   William H. Wehrmacher, M.D., Chicago, Ill.
4. The Feasibility of Anticoagulant Therapy in Coronary Artery Disease with Congestive Heart Failure.
   Ralph M. Tandowsky, M.D. and Walter A. Flieg, M.D., Hollywood, Calif.
5. To be read if time permits: Cholesterol Cripples.
   G. Douglas Talbott, M.D., Dayton, Ohio.
6. Antagonists of Digitalis Toxicity—Experimental Studies.
   E. T. Angelakos, M.D. and H. I. Hurwitz, B.S., Boston, Mass.
7. Newer Methods of Medical Treatment of Coronary Insufficiency.
   Rudolph E. Fremont, M.D., Brooklyn, N. Y.

Annual Business Meeting

Thursday, May 26, 4:30–5:30 p.m.

Fourth Scientific Session

Friday, May 27, 9:00–12:30 a.m.

Symposium on
RECENT ADVANCES IN THE TREATMENT OF CONGESTIVE HEART FAILURE*

Moderator: Kenneth G. Kohlstaedt, M.D., Indianapolis, Ind.

1. Changing Concepts of Mechanism.
   Richard H. Lyons, M.D., Syracuse, N. Y.
2. Use of Cardiac Glycosides.
   Richard J. Bing, M.D., Detroit, Mich.
3. Fluid and Electrolyte Metabolism.
   John H. Moyer, M.D., Philadelphia, Pa.

10:30–11:00 a.m.—Intermission

4. Diuretics and Other Measures.
   E. Hugh Luckey, M.D., New York, N. Y.

Fifth Scientific Session

Friday, May 27, 2:00–5:30 p.m.

SURVEY OF THE DIAGNOSIS AND TREATMENT OF CONGENITAL HEART DISEASE

Moderator: Osler Abbott, M.D., Atlanta, Ga.

1. Diagnosis of Acyanotic Congenital Heart Disease.
   Benjamin M. Gasul, M.D., Chicago, Ill.
2. Diagnosis of Cyanotic Congenital Heart Disease.
   Henry A. Zimmerman, M.D., Cleveland, Ohio.

3:00–3:30 p.m.—Intermission

* Presented by the American Heart Association.

3. Surgical Treatment and End Results in Acyanotic Congenital Heart Disease.
   ROBERT P. GLOVER, M.D., Philadelphia, Pa.
4. Surgical Treatment and End Results in Cyanotic Congenital Heart Disease.
   HARRIS B. SHUMACKER, JR., M.D., Indianapolis, Ind.

Groedel Memorial Lecture on Humanities in Medicine

Friday evening, May 27

The Humanities in Medicine.
JOHN B. YOUMANS, M.D., Washington, D. C.

Sixth Scientific Session

Saturday, May 28, 9:00–12:30 a.m.

Symposium on
EXTREME HYPOTHERMIA IN CARDIAC SURGERY

Moderator: IVAN BROWN, M.D., Durham, N. C.

1. Experimental and Clinical Experience with Perfusion Hypothermia.
   W. GLENN YOUNG, M.D., Durham, N. C.
2. Cardiac Physiology During Hypothermia.
   E. T. ANGELAKOS, M.D., Boston, Mass.
3. Metabolic and Functional Aspects of the Hypothermic Heart.
   JACK J. GREENBERG, M.D., Bethesda, Md.

10:20–10:50 a.m.—Intermission

Moderator: HARRIS B. SHUMACKER, JR., M.D., Indianapolis, Ind.

4. Regional Hypothermia.
   VINCENT L. GOTT, M.D., Minneapolis, Minn.
5. Experiences with Perfusion Hypothermia.
   BRUCE JOHNSTON, M.D., San Francisco, Calif.

Scientific Exhibits

The Effect of the Cardiac Arrhythmias on the Regional Circulation of the Vital Organs. ELIOT CORDAY, M.D., Los Angeles, Calif.

From Parenteral Digitalization to Oral Maintenance. ROBERT B. CROUCH, M.D., Houston, Texas.

Conditioned Renal Responses. SAMUEL A. CORSON, PH.D., ELIZABETH O'LEARY CORSON, PH.D. and ROSCOE A. DYKMAN, PH.D., New Haven, Conn.

Clotting Mechanism. E. R. GABRIELI, M.D., Buffalo, N. Y.

The Precordial Electrocardiogram During Exercise. ALVIN H. FREIMAN, M.D., RAMON ABARQUEZ, M.D., FREDERICK REICHEL, M.D. and JOHN S. LADUE, M.D., New York, N. Y.

Diuresis in Congestive Heart Failure. MORTON FUCHS, M.D., Philadelphia, Pa.

The Circulation During Hypotension (Shock). MAX H. WEIL, M.D., Los Angeles, Calif.

Observations in the Vascular System Associated with Bowel Function. ALFRED HALPERN, PH.D., PAUL H. KUHN, M.D., SAUL S. SAMUELS, M.D., NORMAN SHAFTEL, M.D., HERBERT SHAFTEL, M.D. and DAVID SELMAN, M.D., New York, N. Y.

1960 Honors List

Groedel Medalist
Groedel Memorial Lecturer

JOHN BARLOW YOUMANS, A.B., M.S., M.D., F.A.C.P., Col. U. S. Army (Ret.), Legion of Merit, Legion of Honor, Technical Director of Research for the Army's Research and Development Command, Washington, D. C. Physician, research scientist, scholar, teacher, author, editor, administrator, sportsman, space-man and music afficiando; warms both hands at life's numerous fires, making many of them burn the brighter.

Honorary Fellowship

HELEN BROOKE TAUSSIG, A.B., Phi Beta Kappa, M.D., Alpha Omega Alpha, Associate Professor of Pediatrics in the Johns Hopkins Hospital and Director of Children's Heart Clinic, Harriet Lane Home, Baltimore, Md. Diligent diagnostician, generous teacher, savior of countless ill-fated children.

Honorary Fellowship

GEORGE RUDOLPH HERRMANN, B.S., M.S., PH.D., M.D., Professor of Medicine, Head of the Department of Medicine and Director of the Cardiovascular Research Lab. and Heart Station of the University of Texas, School of Medicine, Galveston, Texas. Pupil of Christian and of Wilson, tireless investigator for more than thirty years. Beloved preceptor of thousands of loyal students.

Honorary Fellowship

MICHAEL ELLIS DEBAKEY, B.S., Sigma Xi, M.D., Alpha Omega Alpha, F.A.C.S., Legion of Merit, Professor of Surgery and Chairman of the Department of Surgery, Baylor University, College of Medicine, Houston, Texas. Soldier, physician, administrator, ingenious investigator, creative surgeon, dauntless and indefatigable surmounter of the impossible barrier.

Convention Neurosis

In Spring a young man's fancy turns to love, the cardiologist's to conventions. Medical meetings are now held on land and sea, probably, soon in the air. Before long reservations will be made for the First Intergalactic Martian Congress of Space Cardiology!

The usual travel hazards of medical conventions are recognized by the sophisticates of the convention circuit. Less serious ones include transportation difficulties and delays, poor accommodations and last minute emergencies. More serious are the medical complications of conventions—strained arches, muscular aches and pains, blisters and even heart attacks from unaccustomed activity, exercise and stress on the boardwalk at Atlantic City, the lake shore in Chicago or the slopes of San Francisco. The incidence of motion sickness, diarrhea and similar disorders will undoubtedly increase as more conclaves are conducted all over the world.

A discussion of the hazards of such meetings is incomplete without mentioning the danger of conference neurosis. I experienced a mild attack of this psychic malady at the 1959 joint meeting of the American Heart Association and the American College of Cardiology in Philadelphia. I was able to diagnose a similar condition in a goodly number of my medical colleagues at the meeting.

The syndrome includes a slight tachycardia, occasional extrasystoles, some flushing of the face and a free-floating irrational anxiety, easily relieved by a therapeutic trial of alcohol or a sample of the latest tranquilizer. The etiology is obviously a stress situation which frequently disturbs the conscientious conference goer at large meetings. These meetings are full of overwhelming accumulations of data, ideas, instrumentation and information, often conflicting. Long accepted and cherished concepts and beliefs are exposed to a barrage of new viewpoints which traumatize the psyche. Fatigue, lack of time and the simultaneous scheduling of interesting events so often seen at conventions further tend to induce a schizophrenic reaction.

The average clinical cardiologist, doing some soul-searching, asks how much of this information is statistically valid, fundamentally worthwhile and personally useful. He quickly realizes he has neither the funds nor the resources to try the newer technics at home. Often, with a sinking heart, he concludes he cannot completely assimilate all the advances in physiology, biochemistry or instrumentation presented at the conference.

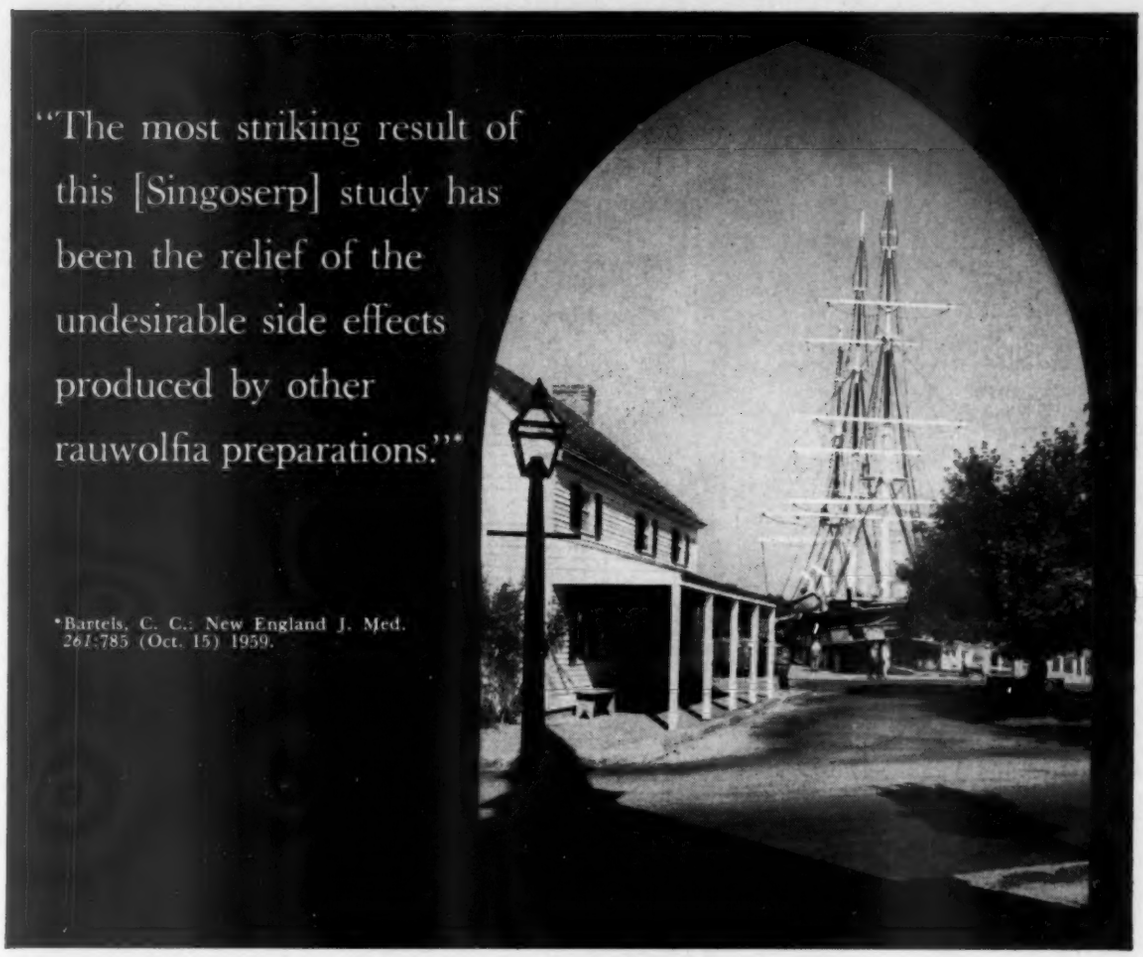
Partially responsible for this difficulty is the basic trend in cardiology for narrower specialization within the specialty in the quest for greater certainty and security. More and more is being written on less and less. Poorly planned panels also aggravate the conference neurosis. Experts may have to prove their expertness by disagreeing with everyone else on the panel. This produces some effective humorous sally but, more often than not, disturbs the listener in his search for new knowledge.

Now, six months later, I view the convention neurosis with a less jaundiced eye. The healing balm of time, my familiar home environment and the leisurely study of The American Journal of Cardiology have ameliorated the anxieties and annoyances aroused at such conventions. Perhaps this is the way medical knowledge advances and grows. Even though one cannot immediately evaluate or utilize all information available at a convention, exposure to new facts is important and understanding may follow.

These thoughts suggest that careful study of medical conventions, sociologically and psychologically, might produce important data on the improvement of the education, training and development of physicians. The necessity for conference feedback is apparent. Better planning of conference panels, lectures, scientific sessions and exhibits should reduce the anxieties and frustrations of the convention neurosis.

Raymond Harris, M.D., F.A.C.C.
Assistant Editor
The American Journal of Cardiology

from the New England Journal of Medicine:



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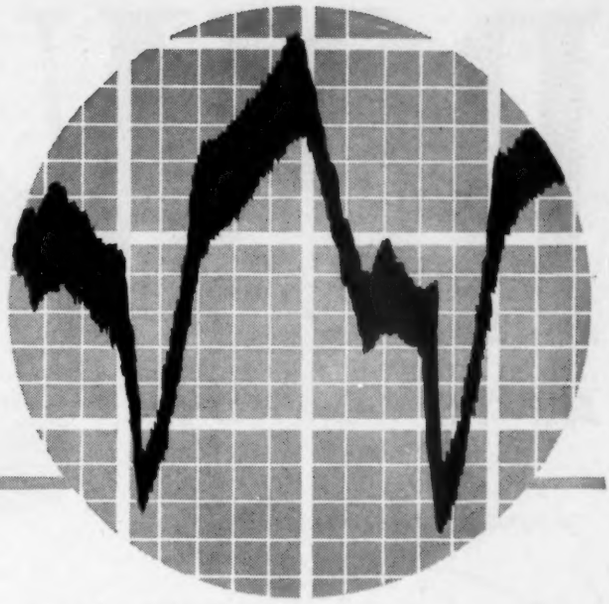

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1. Armbrust, C.A., Jr., and Levine, S.A.: Paroxysmal Ventricular Tachycardia: A Study of 107 Cases. Circulation 1:28 (1950)
2. Bell, G.D., Bradley, R.B., and Hurxthal, L.M.: Paroxysmal Tachycardia, Experiences with Massive Doses of Quinidine Intravenously in a Refractory Case. Circulation 1:939 (1950)

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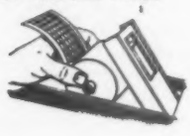

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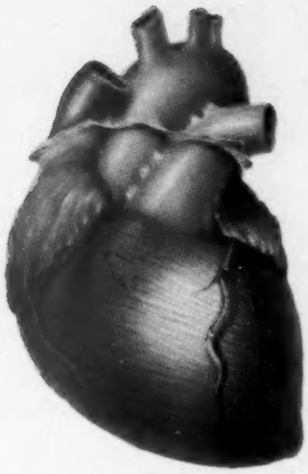
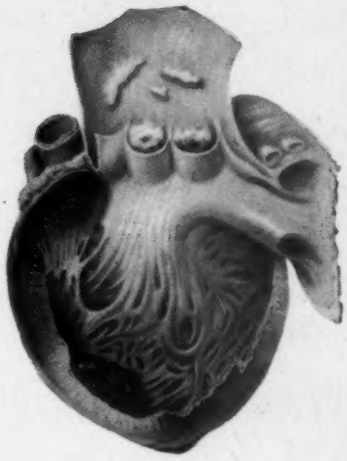


IN ANGINA PECTORIS AND CORONARY INSUFFICIENCY

... the treatment must go further than vasodilation alone. It should also control the patient's ever-present anxiety about his condition, since anxiety itself may bring on further attacks.



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Unless the coronary patient's ever-present anxiety about his condition can be controlled, it can easily induce an anginal attack or, in cases of myocardial infarction, considerably delay recovery.

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Dosage: 1 or 2 tablets q.i.d. *before meals* and at bedtime, according to individual requirements.

REFERENCES

1. Ellis, L. B. *et al.:* Circulation *17*:945, May 1958. **2.** Friedlander, H. S.: Am. J. Cardiol. *1*:395, Mar. 1958. **3.** Riseman, J.E.F.: New England J. Med. *261*:1017, Nov. 12, 1959. **4.** Russek, H. I. *et al.:* Circulation *12*:169, Aug. 1955. **5.** Russek, H. I.: Am. J. Cardiol. *3*:547, April 1959. **6.** Tortora, A. R.: Delaware M. J. *30*:298, Oct. 1958. **7.** Waldman, S. and Pelner, L.: Am. Pract. & Digest Treat. *8*:1075, July 1957.

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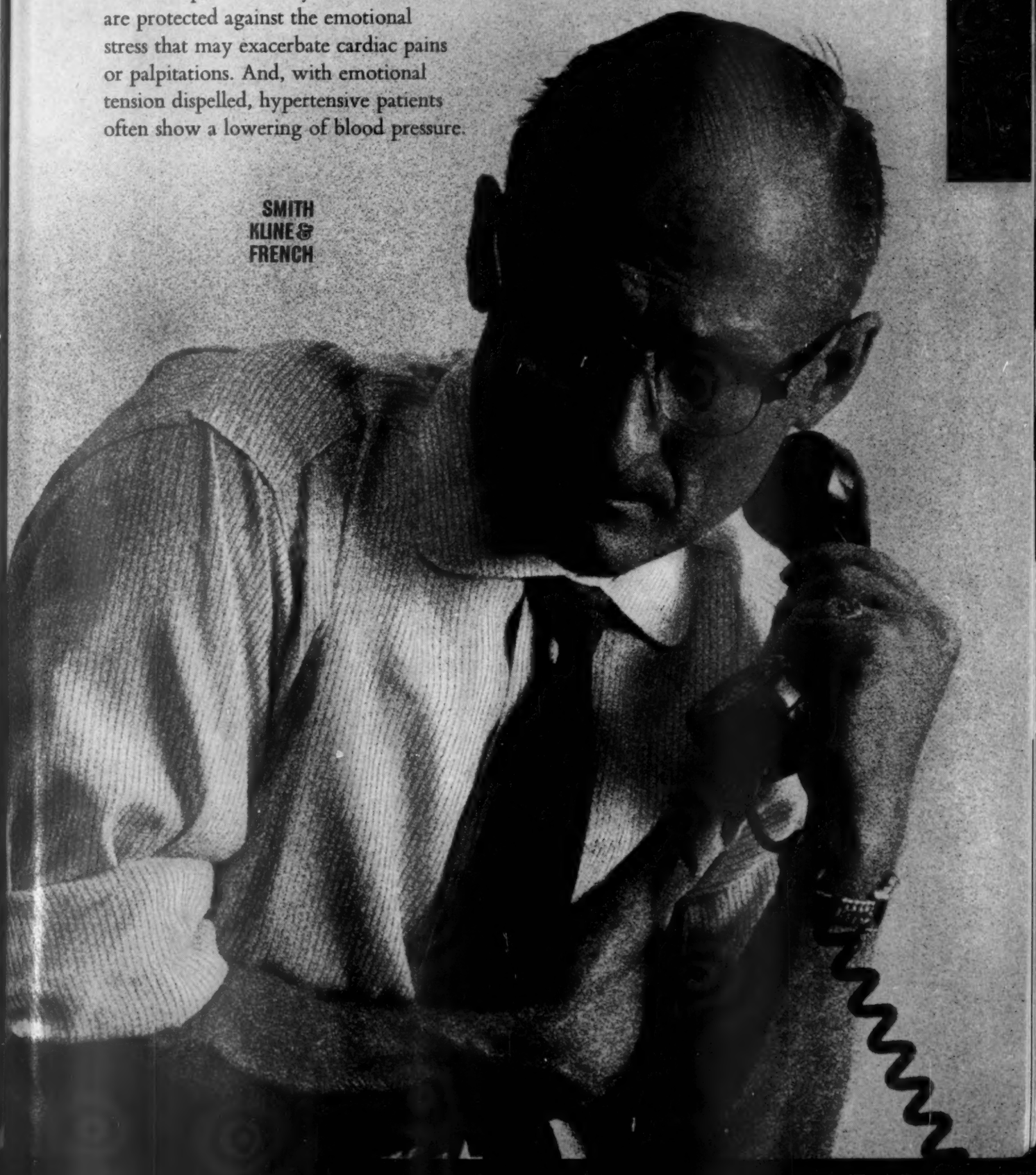

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References: 1. Russek, H. I.: Postgrad. Med. 19:562 (June) 1956. 2. Russek, H. I.: Presented at the Symposium on the Management of Cardiovascular Problems of the Aged, Dade County Medical Association, Miami Beach, April 12, 1958.

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Cereal Institute, Inc.: Breakfast Source Book. Chicago: Cereal Institute, Inc., 1959.
Food & Nutrition Bd.: Recommended Dietary Allowances, Revised 1958. Natl. Acad. Sci.—Natl. Research Council Publication 589, 1958.
Watt, B. K., and Merrill, A. L.: Composition of Foods—Raw, Processed, Prepared. U.S.D.A. Agriculture Handbook No. 8, 1950.

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1. Riseman, J.E.F., *et al.*: Circulation *17*:22 (Jan.) 1958.

2. Russek, H.I.: Circulation *18*:774 (Oct.) 1958.

3. Hirshleifer, I., *et al.*: Scientific Exhibit, A.M.A., Atlantic City, N. J., June, 1959.

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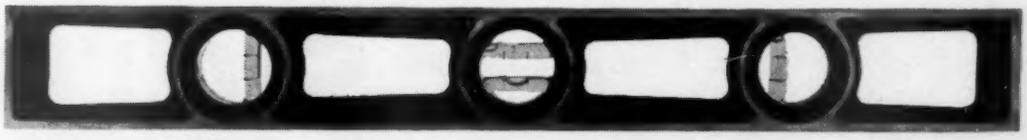

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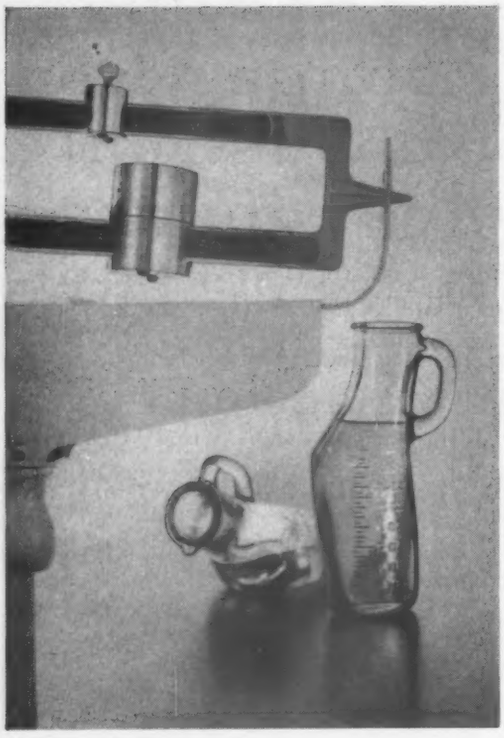

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1. Feinblatt, T. M., and Ferguson, E. A.: New Eng. J. Med. 256:331 (Feb.) 1957.
2. Kupersmith, I. H.: International Record of Medicine, Vol. 171 No. 10 (Oct.) 1958.
3. Berry, J. W., and Roach, T. C.: Circulation, Vol. 17, No. 6 (June) 1958.

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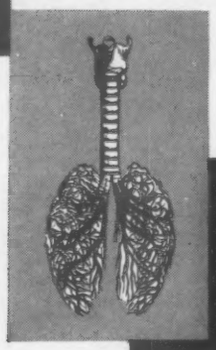

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PERMITIL®

Fluphenazine dihydrochloride

■ In 608 patients with anxiety and anxiety-induced fatigue or depression, PERMITIL, administered in small daily doses of 0.5 mg. to 1 mg., produced significant improvement in 90%.*

■ PERMITIL is virtually free from side effects at recommended dosage levels.

■ Patients become calm without being drowsy and normal drive is restored.

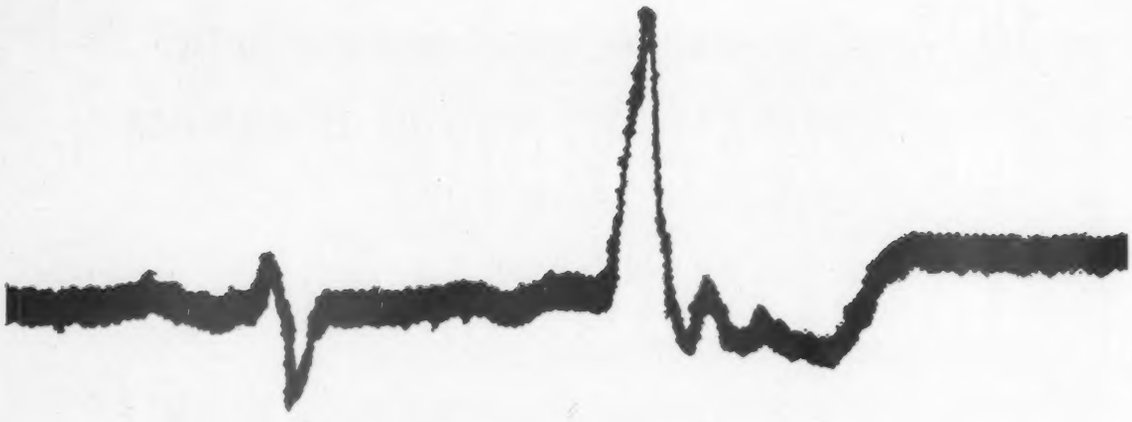
■ Onset of action is rapid; effect is prolonged. ■ PERMITIL does not potentiate barbiturates or non-barbiturate sedatives and can be used with impunity with such agents.

How to Prescribe PERMITIL: The lowest dose of PERMITIL that will produce the desired clinical effect should be used. The recommended dose for most adults is one 0.25 mg. tablet twice a day (taken morning and afternoon). Increase to two 0.25 mg. tablets twice a day if required. Total daily dosage in excess of 1 mg. should be employed only in patients with relatively severe symptoms which are uncontrolled at lower dosage. In such patients, the total daily dose may be increased to a maximum of 2 mg., given in divided amounts. Complete information concerning the use of PERMITIL is available on request.

Supplied: Tablets, 0.25 mg., bottles of 50 and 500.

*Recent compilation of case reports received by the Medical Department, White Laboratories, Inc.

White WHITE LABORATORIES, INC., *Kenilworth, New Jersey*



for cardiac arrhythmias... obvious advantages

PRONESTYL® HYDROCHLORIDE

SQUIBB PROCAINE AMIDE HYDROCHLORIDE

Pronestyl offers obvious advantages over quinidine and procaine in the management of cardiac arrhythmias: "Procaine amide [Pronestyl] should be the drug of choice in arrhythmias of ventricular origin." [1]—on oral administration, side effects are less marked than with quinidine—administered I. V., Pronestyl is safer than a corresponding I.V. dose of quinidine—administered I. M., Pronestyl acts faster than I. M. quinidine[2]—Pronestyl sometimes stops arrhythmias which have not responded to quinidine[3,4]—Pronestyl may be used in patients sensitive to quinidine—more prolonged action, less toxicity, less hypotensive effect than procaine—no CNS stimulation such as procaine may produce.

Supply: For convenient oral administration: Capsules, 0.25 gm., in bottles of 100.
For I. M. and I. V. administration: Parenteral Solution, 100 mg. per cc., in vials of 10 cc.

References: 1. Zapata-Diaz, J., et al.: Am. Heart J. 43:854, 1952. 2. Modell, W.: in Drugs of Choice, C.V. Mosby Co., St. Louis, 1958, p. 454. 3. Kayden, H. J., et al.: Mod. Concepts Cardiovasc. Dis. 20:100. 1951. 4. Miller, H., et al.: J.A.M.A. 146:1004, 1951.

SQUIBB *Squibb Quality—the Priceless Ingredient*

announcing a major event in anticoagulant therapy...

Schering

Certified—before introduction—by 5 years of clinical experience and published reports in the U.S.A., Canada and Great Britain.

Miradon®

anisindione

new oral prothrombin depressant

control at every stage of anticoagulant therapy **rapidity** of induction and recovery time **predictability** of initial and maintenance dosages **stability** of therapeutic prothrombin levels during maintenance therapy **reversibility** of anticoagulant effect with vitamin K_1 preparations... rapid return to therapeutic levels on remedication

Well tolerated and relatively nontoxic no nausea and vomiting, proteinuria, agranulocytosis or leukopenia yet observed —chromaturia infrequent and transient.

Single daily dose convenience

Packaging—MIRADON Tablets, 50 mg., bottle of 100.

For complete information on indications, dosage, precautions, and contraindications consult the Schering Statement of Directions.

S-435

Cardiovascular patients respond in a few days. Thanks to your prompt treatment and the smooth action of Deprol, his depression is relieved and his anxiety calmed – *often in two or three days.* He eats well, sleeps well and his depression no longer complicates your basic regimen.

Lifts depression...as it calms anxiety!

For cardiovascular patients–a smooth, balanced action that lifts depression as it calms anxiety...rapidly and safely

Balances the mood–no "seesaw" effect of amphetamine-barbiturates and energizers. While amphetamines and energizers may stimulate the patient – *they often aggravate anxiety and tension.* And although amphetamine-barbiturate combinations may counteract excessive stimulation – *they often deepen depression.*

In contrast to such "seesaw" effects, Deprol lifts depression as it calms anxiety – both at the same time.

Acts swiftly–the patient often feels better, sleeps better, within two or three days. Unlike most other antidepressant drugs, Deprol relieves the patient quickly – often within two or three days.

Acts safely – no danger of hypotension. Deprol does not cause hypotension, tachycardia, jitteriness, or liver toxicity. It can be safely administered with basic cardiovascular therapy.

Dosage: Usual starting dose is 1 tablet q.i.d. When necessary, this may be gradually increased up to 3 tablets q.i.d.
Composition: 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl) and 400 mg. meprobamate.
Supplied: Bottles of 50 light-pink, scored tablets. Write for literature and samples.

Deprol

WALLACE LABORATORIES
New Brunswick, N. J.

CD-763

"First in the hearts" of cardiac patients

A.C.M.I.

CARDIAC CATHETERS

A.C.M.I. was the first to introduce nylon woven catheters in the United States – originally for ureteral use – later for cardiac catheterization.

A.C.M.I.'s nylon woven cardiac catheters are preferred for smoothness combined with flexibility. Lengths: 30 cm. to 150 cm. Thin-walled, radiopaque.

A.C.M.I.'s polyethylene cardiac catheters provide a smoother and larger lumen for collection of blood samples and the rapid injection of contrast media. Other types too are under development.

A triumph of technical skill – all A.C.M.I. cardiac catheters have earned the confidence of the medical profession through their consistently superior quality.

Nylon woven cardiac catheters

A·C·M·I TRADE MARK

FREDERICK J. WALLACE, *President*

American Cystoscope Makers, Inc.

8 PELHAM PARKWAY, PELHAM MANOR, N. Y.

after a myocardial infarction
and throughout the course
of postcoronary convalescence...

Peritrate helps establish and sustain collateral circulation

1. improves coronary blood flow with no significant drop in blood pressure or increase in pulse rate
2. helps support natural healing and repair
3. helps reduce myocardial damage
4. smooth onset of action minimizes nitrate headache

basic therapy in coronary artery disease

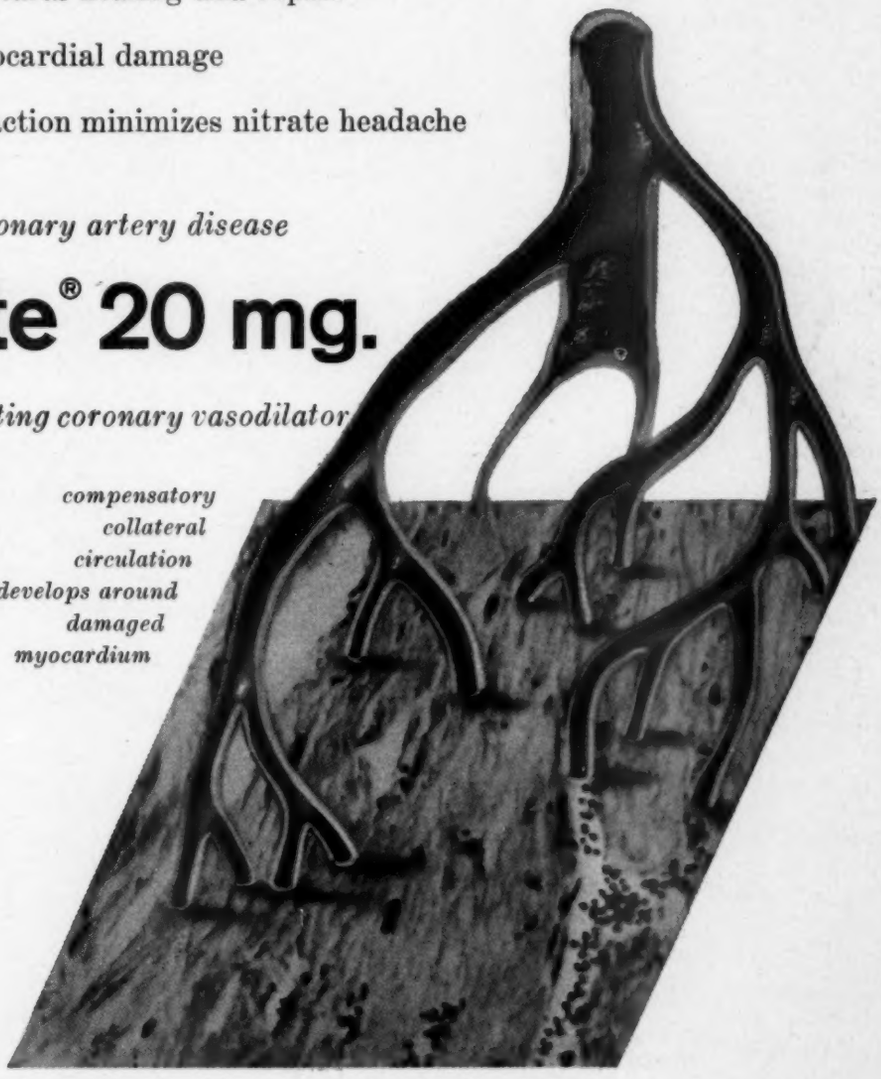
Peritrate® 20 mg.

brand of pentaerythritol tetranitrate

the selective, long-acting coronary vasodilator

WARNER
CHILCOTT
MORRIS PLAINS, N.J.

GP-02



compensatory collateral circulation develops around damaged myocardium

Advertisers' Products Index

May, 1960

*** Complete description of starred drugs will be found in MODERN DRUGS and THE MODERN DRUG ENCYCLOPEDIA**

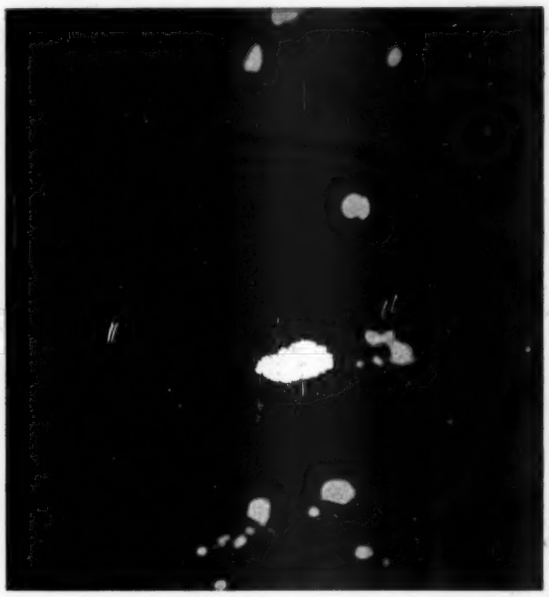
ADVERTISING REPRESENTATIVES

New York: P. D. Brewer, H. S. Schultz, A. K. Detwiller —MUrray Hill 3-2980

Chicago: R. H. Andrew, C. P. Haffner —WAbash 2-7738

Clarin* can do this for your postcoronary patients

WITHOUT CLARIN, turbid blood serum five hours after a fat meal: This unretouched dark-field photomicrograph (2500X) shows potentially hazardous fat concentrations circulating in the blood stream of a patient after a standard fat meal.



WITH CLARIN, clear blood serum five hours after a fat meal: After eating a standard fat meal as at left, the same patient has taken one sublingual Clarin tablet. Note marked clearing effect and reduction in massive fat concentrations in this unretouched photomicrograph (2500X).

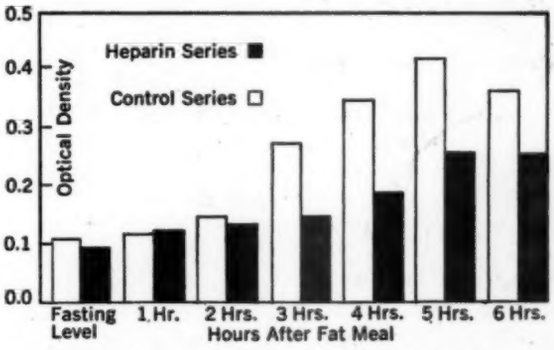
CLARIN is sublingual heparin potassium. One mint-flavored tablet taken after each meal effectively "causes a marked clarification of postprandial lipemic serum."[1] Clarin facilitates the normal physiologic breakdown of fats, with no effects on the blood-clotting mechanism.[1] It therefore provides important benefits for your postcoronary patients.

Indication: For the management of hyperlipemia associated with atherosclerosis.

Dosage: After each meal, hold one tablet under the tongue until dissolved.

Supplied: In bottles of 50 pink, sublingual tablets, each containing 1500 I.U. heparin potassium.

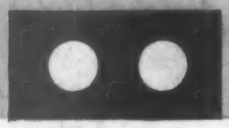
1. Fuller, H. L.: Angiology *9*:311 (Oct.) 1958.
2. Shaftel, H. E., and Selman, D.: Angiology *10*:131 (June) 1959.



Average serum optical density in 36 patients after fat meal with and without sublingual heparin.[2]

*Registered trade mark. Patent applied for.

Thos. Leeming & Co., Inc. New York 17, N. Y.

Just two tablets  *at bedtime*

RAUWILOID®

alseroxylon, 2 mg.

...does more than lower blood pressure!

Seven years of experience show that RAUWILOID also affords

Safety based on negligible incidence of side actions

Freedom from concern over sudden hypotensive episodes or unwanted biochemical alterations

Practicality.. simplicity of dosage ..applicable to a wide range of patients

When more potent drugs are needed, prescribe one of the *convenient single-tablet combinations*

Rauwiloid® + Veriloid®
alseroxylon 1 mg. and alkavervir 3 mg.

or

Rauwiloid® + Hexamethonium
alseroxylon 1 mg. and hexamethonium chloride dihydrate 250 mg.

Many patients with severe hypertension can be maintained on Rauwiloid alone after desired blood pressure levels are reached with combination medication.

Riker

Northridge, California